ISSN 0001-6349

cta Obstetricia et Gynecologica candinavica

. 57 1978 No 1

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SCANDINAVIAN ASSOCIATION OF OBSTETRICIANS AND GYNAECOLOGISTS
by
ALMQVIST & WIKSELL PERIODICAL COMPANY Stockholm, Sweden

Acta Obstetricia et Gynecologica Scandinavica

Official organ of the Scandinavian Association of Obstetricians and Gynæcologists

Acta Obstetricia et Gynecologica Scandinavica

publishes original papers and articles on clinical and experimental research work in the fields of obstetrics and gynecology It brings you the best up to date information on developments and recent progress in these medical fields in the Northern countries

The articles are published in English Denmark Finland Iceland Norway and Sweden are represented on the Editorial Board the Swedish representative being Editor in Chief

Subscriptions

Acta Obstetricia et Gynecologica Scandinavica is published five times annually, each issue containing towards 100 pages Five issues constitute one volume

per volume Sw kr 220 incl postage

Swedish subscribers Add V.A T

Supplements free

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Umeå University Hospital
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Subscription and Circulation

The Almqvist & Wiksell Periodical Company
P O Box 62
S-101 20 Stockholm 1, Sweden
Postal giro account 50464 7

Printers

Almqvist & Wiksell Tryckeri AB
S 751 81 Uppsala Sweden

Acta Obstetricia et Gynecologica Scandinavica

Published by

The Nordic Association for Obstetrics and Gynecology

Editor

Professor Ingemar Joelsson

Address

Box 443 S-901 09 Umeå Sweden

Vol 57, 1978

Printed in Sweden by
Almqvist & Wiksell Uppsala 1978

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ACID AND ALKALINE PHOSPHATASE IN AMNIOTIC FLUID IN NORMAL AND COMPLICATED PREGNANCY

Gunhild Beckman Lars Beckman and Tord Löfstrand

From the Departments of Obstetrics and Gynaecology and Medical Genetics University of Umeå Umeå Sweden

bstract 171 samples of amniotic fluid were obtained by bdominal amniocentesis from 67 women with compli ated pregnancies (isoimmunization diabetes mellitus or ıxaemia) The levels of heat labile alkaline phosphatase AP) heat stable alkaline phosphatase (HSAP) and cid phosphatase (AcP) were determined and compared to ıe enzyme levels in 179 samples from women with nor ıal pregnancies of corresponding gestational ages HLAP howed two peaks of activity one in the 15th–22nd eek and the other at term HSAP and AcP showed in reased activity at term HSAP was decreased ($p<0.01$) in ıoimmunization between the 36th and 40th week 11 of toxaemia with placental insufficiency showed no ifferences in the levels of HLAP and HSAP compared normal pregnancy AcP showed no differences be ween normal and complicated pregnancy Samples con aminated by blood showed no significant increase in the cid and alkaline phosphatase levels Samples contami ated by meconium showed a complex pattern Some had normal enzyme levels some had high levels f HLAP only and some had high levels of HSAP and AcP The origin of the enzymes is not known with cer ainty HSAP in amniotic fluid is most likely not of placen al but of intestinal origin Determinations of acid and al aline phosphatase in amniotic fluid seem to be of little alue in the clinical management of complicated preg ıancy

In erythroblastosis Geyer & Schneider (5) found d levels of acid phosphatase (AcP) and al aline phosphatase (AP) Roopnarinesingh et al 11) observed an increase of heat stable alkaline phosphatase (HSAP) in pre eclampsia Fennefrohn 3) suggested that an AP level above 10 KA units ndicates fetal maturity while >20 KA units is indi ative of fetal growth retardation and placental in ufficiency Benzie et al (2) found normal values of AcP and AP in intrauterine growth retardation iabetes Rh immunization hydramnios and hy ertensive disorders

Several authors have attempted to determine the origin of AcP and AP in amniotic fluid Sutcliffe & Brock (12) suggested that at term AcP originates both from the surrounding tissues and from fetal urine Concerning the origin of AP there are con flicting views The results of Sutcliffe & Brock (12) and Jonasson (7) indicate that HSAP in amniotic fluid is of placental origin However Kellen et al (8) and Hahnemann & Sørensen (6) claim that this is not the case

This paper reports the results of a study on HLAP HSAP and AcP in normal pregnancy and in pregnancy complicated by isoimmunization dia betes mellitus or toxaemia

MATERIAL AND METHODS

The normal material consists of 179 samples from 170 pregnant healthy subjects 171 samples of amniotic fluid were obtained by abdominal amniocentesis from 67 wom en with complicated pregnancies in the 27th–43rd week Samples containing macroscopically detectable blood or meconium were discarded only clear fluid was accepted Diagnostic criteria for pregnancy complications and for estimation of gestational age have been presented previ ously (4 9 10)

The amniotic fluid was centrifuged filtered through filterpaper and stored at −18 C until enzyme analysis AcP and AP were determined according to methods previously described (1) To identify different isoenzymes in the amniotic fluid double-diffusion techniques and starch gel electrophoresis were used

RESULTS

In Tables I–III data for normal and complicated pregnancies have been divided into four periods according to gestational age HLAP showed significant differences between consecutive periods (Table I) HSAP showed a significant increase for

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Table I *Heat labile alkaline phosphatase activity in amniotic fluid (μmol α-naphthol liberated per ml per h) in normal pregnancies and pregnancies complicated by immunization diabetes and toxaemia*
Figures within brackets indicate number of samples examined Mean ±S D

Pregnancy week	Normal pregnancy	Pregnancy complicated by Immunization	Diabetes	Toxaemia
30 and earlier	1 58±1 22 (47)	0 23±0 16 (10)	–	–
31–35	0 35±0 29 (34)	0 34±0 19 (29)	0 84±2 00 (13)	0.36±0 44 (20)
36–40	1 25±1 07 (74)	1 68±5 06 (51)	0 76±0 80 (21)	2 31±4.56 (25)
41 and later	3 34±3 01 (74)	–	–	4 75±1 45 (7)

the three first periods and then a non significant decrease (Table II) AcP increased significantly from the third to the fourth period (Table III)

When comparing the enzyme levels in normal pregnancy with those in complicated pregnancy a significant decrease in HSAP activity was found in isoimmunization in the 36th–40th week ($p<0.01$) The difference in HLAP level between normal pregnancy and isoimmunization before the 31st week was highly significant ($p<0.001$) but trivial Samples from pregnancies before the 27th week where the HLAP level is high were lacking among the pregnancies complicated by isoimmunization AcP showed no difference between normal and complicated pregnancy

The effect of contamination by blood or meconium in full term pregnancies is shown in Table IV In samples contaminated by blood the average enzyme levels were not significantly increased In samples macroscopically contaminated by meconium the average levels of all three enzymes were significantly increased when compared to the levels for normal pregnancy Meconium contaminated samples however showed a complex pattern 9 of the 23 samples showed normal activity of all three enzymes 12 samples had high levels (>10 μmol) of HLAP 6 of these also had high levels (>5 μmol) of HSAP The remaining 2 samples showed high activity of HSAP but low levels of HLAP The 8 samples with high levels of HSAP had high levels of AcP Table V shows the correlation between AcP and HSAP in the meconium contaminated samples Thus samples with an AcP level above 0 3 μmol showed a fourteenfold increase of the HSAP level compared to samples with an AcP level below 0 3 μmol In this connection will be mentioned that 4 samples of amniotic fluid from normal pregnancy are not accounted for in the Tables These 4 samples showed very high AP values 10 S D s above the mean of the other 29 samples of the same gestational age (weeks 39–4?) Two of these samples were cloudy two were ?? In double-diffusion experiments in agarose samples with high levels of HSAP reacted with an antiserum prepared against purified placental AP The precipitation lines showed AP activity Extracts of amniotic cells showed no reaction with the abovementioned antiserum In previous experiments this antiserum has been shown to react with AP from placenta and intestine but not from liver

Samples with high enzyme levels were examined by starch gel electrophoresis and subsequent enzyme staining It was not possible to distinguish HSAP and HLAP electrophoretically All samples

Table II *Heat stable alkaline phosphatase activity in amniotic fluid (μmol α-naphthol liberated per ml and h) in normal pregnancies and pregnancies complicated by immunization diabetes and toxaemia*
Figures within brackets indicate number of samples examined Mean ±S D

Pregnancy week	Normal pregnancy	Pregnancy complicated by Immunization	Diabetes	Toxaemia
30 and earlier	0 33±0 29 (47)	0 54±0 25 (10)	–	–
31–35	0 91±0 9? (34)	0 72±0 20 (?9)	1 4?±2 9? (13)	0 8?±0 63 (?0)
36–40	1 25±1 06 (74)	0 80±0 41 (51)	1 05±1 0? (21)	1 43±1 53 (25)
41 and later	1 05±0 71 (?4)	–	–	1 69±0 23 (?)

Table III *Acid phosphatase activity in amniotic fluid (μmol α-naphthol liberated per ml and h) in normal pregnancies and pregnancies complicated by immunization diabetes and toxaemia*

igures within brackets indicate number of samples examined Mean ±S D

Pregnancy week	Normal pregnancy	Pregnancy complicated by		
		Immunization	Diabetes	Toxaemia
0 and earlier	0 076±0 041 (47)	0 109±0 059 (10)	–	–
1–35	0 073±0 035 (34)	0 084±0 053 (?9)	0 108±0 072 (13)	0 087±0 044 (20)
6–40	0 096±0 107 (74)	0 077±0 048 (51)	0 095±0 056 (21)	0 112±0 102 (25)
1 and later	0 196±0 155 (24)	–	–	0 187±0 064 (2)

of amniotic fluid with high levels of AP showed a wide and rather blurred zone of enzyme activity imilar to that found in meconium (Fig 1) The ront of this zone had about the same mobility as AP rom fetal intestine AP in amniotic fluid did not oincide in its electrophoretic mobility with any of he common phenotypes of placental AP Samples of amniotic fluid with high levels of AcP showed one rather strong and blurred zone of activity (Fig) A zone with the same mobility and appearance was found in meconium Extracts of placenta and etal intestine showed different electrophoretic pat erns AP from meconium and fetal intestine was ound to be heat stable

DISCUSSION

The trends as far as acid and alkaline phosphatase levels during normal pregnancy are concerned were in agreement with the findings by Hahnemann & Sørensen (6) and Sutcliffe et al (13)

This study also agrees with that of Geyer & Schneider (5) who found a lowered level of AP in isoimmunization We found a decreased level of HSAP in the period 36th–40th week Other in vestigators however have not confirmed this (2 7) No effect of isoimmunization on AcP was found and thus we were not able to confirm the results of Geyer & Schneider (5)

The observation by Roopnarinesingh et al (11) and Fennefrohn (3) of an increased level of HSAP in toxaemia or placental insufficiency is not supported by our study Their findings might be explained by meconium release especially in cases of fetal dis tress Even slight contamination by meconium may give a pronounced increase in the phosphatase level In our material 11 cases of toxaemia with placental insufficiency showed neither increase nor decrease in the levels of HLAP and HSAP com pared with normal pregnancy

In diabetes mellitus the AcP and AP levels were found to be within normal limits in agreement with previous investigations (8)

Conclusively studies of AcP and AP in amniotic fluid seem to be of little value in the clinical man agement of complicated pregnancy This applies to the estimation of the gestational age as well

It can be questioned whether there may exist

Table IV *Acid and alkaline phosphatase activities n samples of amniotic fluid (μmol α-naphthol lib rated per ml and h) contaminated by meconium and blood (Mean ±S D)*

	Samples contaminated by	
	Meconium (n=?3)	Blood (n=25)
Heat labile alkaline phosphatase	16 57 ±15 15	1 7? ±1 79
Heat stable alkaline phosphatase	8 42 ±11 9	2 78 ±3 47
Acid phosphatase	0 352± 0 343	0 ?48±0 614

Table V *Relation between acid and alkaline phosphatase activity (μmol α-naphthol liberated per ml and h) in samples of amniotic fluid con taminated by meconium (Mean ±S D)*

	Acid phosphatase activity	
	Below 0 3 μmol per ml and h (n=15)	Above 0 3 μmol per ml and h (n=8)
Heat labile alkaline phosphatase	13 97±16 66	21 43±11 08
Heat stable alkaline phosphatase	1 50± 0 92	21 43±12 23

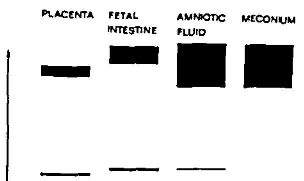


Fig 1 Schematic picture showing the alkaline phosphatase patterns in placenta (S variant) fetal intestine amniotic fluid contaminated by meconium and meconium after starch gel electrophoresis at pH 8 6 The arrow shows the direction of migration towards the anode

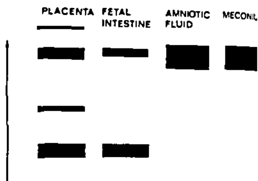


Fig 2 Schematic picture showing the acid phospha[...] patterns in placenta fetal intestine amniotic fluid co[...] taminated by meconium and meconium after starch [...] electrophoresis at pH 8 2 The arrow shows the directi[...] of migration towards the anode

smaller or rather large contributions of enzymes from meconium without any detectable discolouration of the amniotic fluid Jonasson (7) and Hahnemann & Sorensen (6) noticed samples of amniotic fluid with high AP levels but without detectable meconium contamination In this investigation four samples were found in weeks 39–40 with extremely high AP values but without discolouration If they had been included the mean AP level would have been increased almost threefold It may be argued that discarding such extreme values is not allowed But it is well known from amnioscopic or even direct examination of the amniotic fluid that a slight green discolouration is very difficult to de[...] Thus occasional contributions of meconium [...] samples of amniotic fluid may pass unnoticed [...] may strongly influence the results There*fore we think it is correct to discard extreme values* of phosphatase which fall outside the normal distribution since it is very plausible in these cases that contamination of meconium has occurred A technical complication like this will render contradictory results

Concerning the origin of AcP and AP in amniotic fluid different views have been presented Sutcliffe & Brock (12) and Roopnarinesingh (11) suggested HSAP to be of placental origin Changed levels should therefore reflect disturbances in placental function (3 11) Our results indicate however that HSAP in amniotic fluid probably is of intestinal and not of placental origin Electrophoretically AP in amniotic fluid was different from the common placental AP phenotypes Furthermore the strong association between the levels of HSAP and AcP in dicates these enzymes to have a common orig[...] and electrophoretically these enzymes coincid[...] with the patterns found in meconium

It is difficult to explain why HLAP and HSAP [...] meconium contaminated samples appear to be [...] sociated with the same electrophoretic compone[...] The proportions of HLAP and HSAP vary consi[...] erably between samples One possibility may [...] that the time between voiding of meconium a[...] sampling may affect the results so that fresh[...] voided meconium contains HSAP and AcP In ti[...] AP may alter its heat stability e g through the [...] tion of other enzymes in the fluid and AcP m[...] gradually loose its activity

ACKNOWLEDGEMENTS

This investigation was supported by grants from t[...] Swedish Medical Research Council (Project No 0[...] 2725) the Medical Faculty University of Umeå and th[...] Perinatal Research Council of Expressen The skil[...] technical assistance of Mrs Solveig Berggren is grateful[...] acknowledged

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Submitted for publication April 12 1976

Tord Löfstrand
Department of Obstetrics and Gynecology
Kärnsjukhuset
S-54101 Skövde
Sweden



Acta Obstet Gynecol Scand 57 7–11 1978

ORGANIZATION OF AMNIOCENTESIS FOR ANTENATAL GENETIC DIAGNOSIS

Desider J Rothe Lars L Cederqvist Ioannis A Zervoudakis and Fritz Fuchs

From the Department of Obstetrics and Gynecology
The New York Hospital Cornell Medical Center New York N Y USA

Abstract In spite of the rapid development of amniocentesis for genetic diagnosis it is still only a small fraction of the mothers at risk who are having the procedure performed The medical and public health problems associated with genetic amniocentesis are discussed on the basis of the experience gathered in a major medical center

Prenatal diagnosis of fetal disorders on the basis of examination of amniotic fluid was introduced about 25 years ago when Bevis (1952) examined the content of the bile pigment in cases of erythroblastosis fetalis due to Rh isoimmunization of the mother Some years later it was demonstrated that examination of the cells in the amniotic fluid could reveal the fetal sex (11 16 24 25) and the fetal ABO blood group (11) features which both could be used as genetic markers Riis & Fuchs (1960) were the first to use antenatal sex determination for the prevention of sex linked hereditary disorders such as hemophilia and one form of muscular dystrophy Technological advances soon led to attempts to culture amniotic fluid cells for karyotype studies (10) but the first successful reports did not appear until 1966 (26 27) When in the same year it was first predicted that it should be possible to diagnose inborn errors of metabolism before birth by biochemical examination of the amniotic fluid (7) it was not anticipated that ten years later we would be able to diagnose more than 60 different hereditary disorders of this kind This is just another illustration of the rapid development of the medical sciences and we can take some pleasure from the fact that this happened within the specialty of obstetrics But although obstetricians can claim some of the credits for the first inroads in this field the subsequent development would not have been possible without the work of geneticists biochemists and pediatricians And it would not have been possible without the rapid advances in the technology of tissue culture and the development of new biochemical methods particularly in enzymology during the last two decades Nor would it have been possible without the detailed characterization of inherited metabolic disorders moving from a study of their clinical manifestations to the demonstration of specific enzyme deficiencies in various tissues and from there to the recognition of such deficiencies in cultures of fibroblasts leukocytes and amniotic fluid cells

In addition to the inborn errors of metabolism and the chromosomal abnormalities a third group of congenital disorders have been added to those which can be detected before birth the neural tube defects These disorders are characterized by a high concentration of a specific protein α fetoprotein in the amniotic fluid Also the level in the maternal plasma is increased permitting screening for these congenital malformations by examination of maternal blood samples in the beginning of the second trimester of pregnancy (4 17 23)

The advantages of antenatal diagnosis of inborn errors of metabolism chromosomal abnormalities and neural tube defects are quite obvious Many of these disorders lead to severe debilitating disease often with death at an early age Others are associated with severe mental retardation precluding a normal life For most of these disorders no treatment exists as yet but if they can be diagnosed early in gestation the birth of afflicated individuals can be prevented by interruption of the pregnancy However while the prevention is of great advantage both to the individual parents and

Table I *Number of genetic amniocenteses performed*

Numbers in brackets indicate patients aged 35 and over

Year	At New York Hospital Cornell Medical Center	New York City (estimates)	USA (estimates)
1973	20 (258)	200 (7 000)	1 200 (200 000)
1974	74 (?64)	300 (7 000)	3 000 (200 000)
1975	159 (309)	700 (7 000)	5 000 (?00 000)

to society at large the development of the necessary public health measures poses considerable problems Some of these problems are illustrated by our own experience in organizing a program for genetic amniocentesis

Before 1973 the demand for amniocentesis for genetic diagnosis in our institution was very limited and cases were managed on an individual basis In 1973 it became evident that a more systematic approach was necessary A laboratory for culture and karyotyping of amniotic fluid cells was established In the beginning amniocentesis was recommended only to mothers 40 years of age or older and mothers with balanced translocations or with previous children with chromosomal defects Grad ly the availability of amniocentesis for chromo e studies became known and procedures and idelines for referral were developed During the calendar year 1973 only 20 genetic amniocenteses were performed but as Table I illustrates once the laboratory was firmly established the activity increased rapidly 74 procedures were done in 1974 and 159 in 1975 The subsequent tables are based on the experience of these two years

INDICATIONS

When it became evident that the procedure could be carried out with minimal risks even on a fairly large scale we decided to advise all mothers over 37 years of age to have amniocentesis and to perform it even in the age group 35–37 on request in view of the increasing risk of Down s syndrome after 35 (5) As seen in Table II maternal age was by far the most frequent indication Previous delivery of an infant with Down s syndrome only constituted the indication in 10% of the cases The maternal age distribution shown in Table III illustrates that the largest number of reques amniocentesis came from patients between 38 40

PROCEDURE

Amniocentesis is usually performed at 16–17 we of gestation as an out patient procedure With a exceptions all amniocenteses are performed by investigator (DJR) and we no long r accept niotic fluid samples collected by obstetricians their offices unless the patient lives too far to come to the hospital Sonography is usually formed before the procedure for placental local tion but we do not as a rule perform amniocen sis under sonographic control Grossly bloody niotic fluid was obtained in 24% of the taps gardless of whether sonography had been formed or not The amniotic fluid is placed direc into tissue flasks without centrifugation (6) An quot is taken for determination of α fetopro The elimination of separation of the cells from amniotic fluid has reduced the risk of contam tion and increased the growth rate The aver time between amniocentesis and karyotyping now 18 days

Rh negative mothers are given Rh-ogam the procedure unless previously immunized or husband was known to be Rh negative too In of the cases amniocentesis had to be repea failure to yield enough cells for karyotyping patients refused to have a second amniocen and one of these aged 40 subsequently deliver an infant with Down s syndrome

Genetic counseling is an essential feature of program and is provided both by the obstetric geneticist and a genetic counselor An inform consent is always obtained at the initial counsel session with the patient and her husband bu peated time consuming contacts are often nec sary particularly during the interval between niocentesis and diagnosis

Table II *Indications for amniocentesis*

Maternal age	197	84.5
Previous trisomy 21	24	10.3
Neural tube defect	8	3.4
Fetal wastage	2	0.9
Sex determination	1	0.45
Previous congenital abnormalities	1	0.4
Total	233	100.0

ABNORMAL FINDINGS

The abnormal findings included five cases of Trisomy 21 (Down s syndrome) two cases of Trisomy 18 and one case of mosaic Trisomy F (Table IV) In all instances the pregnancy was interrupted at the request of the mother All the aborted fetuses were found to be of the predicted sex a corroboration of the original findings One patient was 48 years old and the pregnancy was her first after interruption of the pregnancy she ceased menstruating and adopted a child

Abnormal chromosomal complement was found in association with normal phenotypes in five cases (Table V) In two cases the fetus carried the same balanced translocation as the phenotypically normal mother In three cases mosaicism and abnormal cell lines were considered most likely due to artefact or viral contamination In two cases female infants were predicted from the chromosome complement but normal male infants were born in both cases amniocentesis was performed by obstetricians in their office and inadvertent puncture of the maternal bladder cannot be ruled out Two errors on a total of 233 examinations gives an accuracy rate of 99%

COMPLICATIONS

Grossly bloody amniotic fluids were as mentioned obtained in 24% of the cases regardless of whether sonography was performed or not One major advantage of sonography is illustrated by the following case A patient requested that amniocentesis be performed without prior sonography to avoid exposure of the fetus to short wave radiation Amniocentesis was performed without complication and a normal female was predicted At 38 weeks she delivered normal twins Sonography would have permitted the early diagnosis of a twin gestation and facilitated the sampling of both amniotic fluids

A 40-year-old patient aborted one week after a

Table III *Distribution of maternal age*

Under 35	29	12 4%
35–37	69	29 3%
38–40	87	37 3%
41–44	45	19.3%
Over 44	3	1 7%
Total	233	100 0%

Table IV *Abnormal findings*

4 cases of	47,XY +21	Trisomy 21 (Down s syndrome)
1	46,XY +(21 15)	Trisomy 21 (Down s syndrome)
1	47,XY +18	Trisomy 18
1	47,XX +18	Trisomy 18
1	46,XY / 47,XY +F	Mosaic Trisomy F

8 cases—3 4% of total amniocenteses performed

repeat amniocentesis Another patient 41 years old aborted 4 weeks after amniocentesis her pregnancy was complicated by uterine fibroids and hypertension and she had previously had five elective abortions One patient delivered a stillborn at 35 weeks 12 weeks after a repeat amniocentesis The first culture showed unusual chromosomal abnormalities compatible with viral infection the second culture revealed a normal chromosomal complement No congenital abnormalities were found at autopsy Thus the total fetal loss was 1 3%

SEQUELAE

When a fetal abnormality is found and the pregnancy is interrupted it puts the parents under considerable psychological stress particularly if the couple does not have any previous normal children Although spared the delivery of a severely affected child the parents have guilt feelings self reproaches depressions and marital strains as has been observed by other investigators (3) The effect of such sequelae can be greatly reduced by intensive post abortion counseling

DISCUSSION

Our results provide evidence that second trimester amniocentesis is a safe and accurate procedure and they are in complete agreement with the collaborative prospective study of the safety and accuracy of genetic amniocentesis carried out under the direction of the National Institute of Child Health and Human Development A recent report on that study of 1040 subjects and 992 controls showed a fetal loss of 3 5% for the subjects and 3 2% for the controls and a diagnostic accuracy of 99 4% (19)

The demand for amniocentesis to detect inborn errors of metabolism (8) has been very limited and

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The demand for amniocentesis to detect errors of metabolism (8) has

Table V *Abnormal karyotypes with normal phenotypes*

Karyotype	Phenotype	Comment
46,XX 5p− 22q+	Normal female with balanced translocation	Mother same translocation
46,XX 1q+ 8q−	Normal female with balanced translocation	Mother same translocation
46,XX / 47,XX+13 11 cells / 1 cell	Normal female	? Contamination
1 46,XY / aneuploidy ranging from 45–47 11 cells / 4 cells	Normal male	
2 46,XY 13 cells	Stillborn male at 3? weeks no congenital abnormalities	? Viral amnionitis
46,XX / 47,XX+E / 46,XX Dq−Cp+ 47 cells / 1 cell / 2 cells	Normal female	? Artefact

not justified the development of a laboratory with the necessary biochemical capabilities We have managed such cases either by referral of the patients to appropriate centers or by sending amniotic fluid samples to laboratories with documented expertise in regard to the disorders in question A more pressing need has been to develop a program for antenatal detection of neural tube defects by determination of α fetoprotein in amniotic fluid and maternal blood the incidence of these congential malformations is almost the same order of magnitude as the incidence of all the detectable genetic disorders together

O ... in developing facilities and exper... for antenatal detection of genetic disorders is ... to that of others (1 12 13 15 18 20) Once the procedures and lines of referral have been established the demand increases rapidly Even so far from all the patients at risk are getting amniocentesis As seen in Table I there were 309 patients aged 35 or over who gave birth in our institution during 1975 but we only performed 159 amniocenteses Not all the patients were seen early enough in pregnancy to have genetic amniocentesis on the other hand some of our amniocenteses were performed on patients who delivered elsewhere For the City of New York the situation was worse with only about 10% of the estimated number at risk having amniocentesis For the country as a whole the estimated figure for 1975 is only 2 5% Although a 1974 survey by Kaback & Levine demonstrated a rapid growth both in the number of centers performing genetic amniocentesis and the number of amniocenteses performed by each center there is a long way to go before all the pa tients at risk have access to the procedure

To cover the population at risk will thus req... the development of a very large number of fa... ties Is it worth the effort? A group of concern... scientists in New York has made a calculation ... the costs for a program for the City (22) The gr... estimated that about 8000 amniocenteses wo... have to be carried out annually to detect and pr... vent 60 cases of Down s syndrome At $?00 pe... amniocentesis and excluding start up costs the an... nual expenditure would be $1 600 000 as compar... to an estimated cost for the lifelong care of 6... cases of Down s syndrome of $12 000 000

Previous studies and our own experience all pro... vide strong support for the view that amniocen... for genetic diagnosis should be organized on a... regional basis Expertise in karyotyping and genet... counseling is scarce and can be best utilized if lo... cated in tertiary centers of obstetric care Whe... necessary however amniotic fluid samples can be shipped over long distances even from one con... nent to another without the cells losing their p... tential for growth in culture (11*a*)

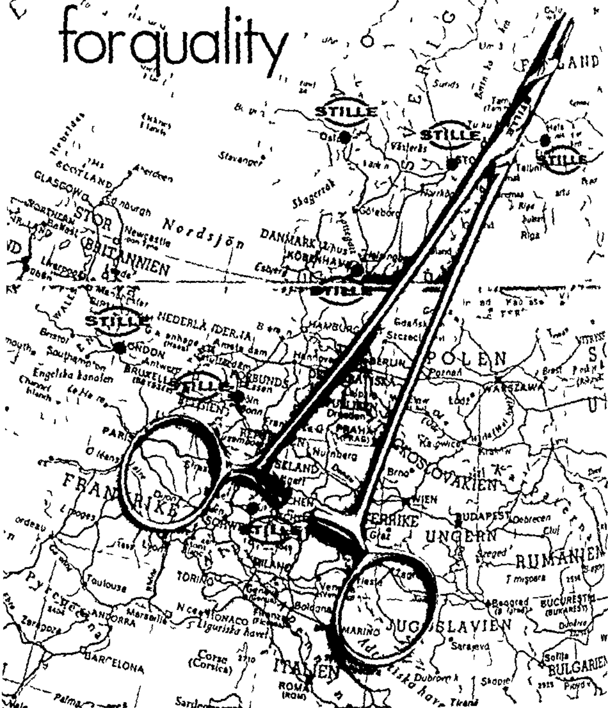
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Submitted for publication Nov 22 1976

Fritz Fuchs
Department of Obstetrics and Gynecology
The New York Hospital Cornell Medical Center
525 East 68th Street
New York NY 10021
USA



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Acta Obstet Gynecol Scand 57 13–18 1978

DIAGNOSTIC AND THERAPEUTIC IMPLICATIONS OF INTRAPARTUM FETAL pH MEASUREMENT

Carl Wood

From the Department of Obstetrics and Gynaecology Monash University The Queen Victoria Memorial Hospital Melbourne Victoria Australia

ostract (1) Measurement of fetal scalp blood pH aids the tection of fetal asphyxia The investigation is done on tients whose fetus is at increased risk of death (?) pecial care in the collection and measurement of scalp ood pH is necessary to obtain satisfactory results A iange of 0 05 pH unit is significant (3) Acidosis is pres it when scalp pH is <7 25 (4) A severe acidosis pH 7 10 indicates a worse fetal prognosis (5) Fetal etabolic acidosis is the commonest type of acidosis but less hazardous than asphyxial acidosis (6) Fetal etabolic acidosis is associated with use of drugs PET tal growth retardation amniotomy and maternal starva on (7) The possibility of transient acidosis needs to be ken into account when interpreting fetal scalp pH meas- rements (8) Fetal scalp blood studies have helped in fining the influence upon fetal condition of maternal yperoxygenation duration of birth maternal posture and ie influence of drugs on fetal condition (9) A controlled ial has shown that fetal intensive care routine FHR ionitoring and selected fetal scalp blood pH measure ient in a high risk group is associated with improved iochemical and neurological status of the newborn (10) ver the last eight years there has been a significant duction of intrapartum anoxic stillbirths at the Queen ictoria Hospital One of the probable reasons for this duction in intrapartum stillbirths is the introduction of tal diagnostic techniques (11) Fetal heart rate monitor g is more help to the clinical obstetrician than scalp ampling—it is applicable both antepartum and in apartum more easily organized and more easily learnt

Methodology

Scalp sampling is mainly used as a means to esti mate fetal blood pH The normal range i e two standard deviations of scalp blood pH is 7 25–45 (7)

The confidence limits of scalp blood pH meas urement 0 05 pH units is twice as large as cord blood (7) The variation of fetal scalp pH is most likely due to the capillary blood varying between arterial and venous blood in its composition Because of the greater variation of measurement change of scalp pH can only be considered relevant when it is more than 0 05 pH unit

For a variety of reasons mean values from different centres differ significantly (6) The mean values from fourteen centres fall into three distinct statistical categories ranging from 7 29 to 7.38 (Table I) Therefore it is important for each hospital to determine their own normal mean and range In our laboratory acidosis has been defined as <7 25 To establish this normal mean we used two criteria population statistics which defined an abnormal population when pH was <7 25 and the Apgar score which also tended to decline when pH was <7 25 (6)

Table I *Variability of pH in different centres*

Mean pH	Studies
7 29–7 30	6
7 32	2
7.35–7 38	6

Table II *Relationship between Apgar score and fetal scalp blood pH*

	No of fetuses with Apgar score		
pH	0–3	4–10	Incidence of Apgar 0–3 (%)
≥7 25	4?	298	1?
<7 25	27	46	37

$\chi^2 = 26$ $P<0\ 001$

Table III *Apgar score and severity of acidosis*

	Apgar score		Incidence apgar
	0–3	4–10	0–3
pH <7 10	12	2	86%
pH 7 10–0 24	15	31	33%

$\chi^2=10\ 5$ $P<0\ 001$

Table IV *Type of acidosis*

	pH	pO_2	O_2 sat %	Apgar score	*n*
Asphyxial	7 10	13	24	4 1	18
Metabolic	7 18	24	43	6 8	20
Normal	7 35	23	53	9 5	12

Table V *Narcotics*

	Maternal pH change	Fetal pH change
Heroin	−0 04	−0 04
Nalorphine	−0 03	−0 03
Morphine	−0 0?	−0 03
Pethidine	−0 02	−0 02

Table VI

	Normal	Hyper tension	Hypertension and proteinuria
n	21	151	88
pH	7 35	7.31	7 28
PCO_2	47	47 5	49
PO_2	23	22	23
BE_p	−0 5	−1 8	−2 9

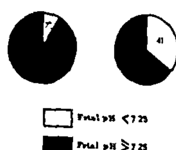


Fig 1 Percentage of patients with pH<7 25 in no... ($n=56$) and low estriol ($n=71$) groups The differ... between the groups was significant $p<0\ 001$

Acidosis and Apgar score

When acidosis is present pH is <7 25 then ... three babies are born with an Apgar ... (Table II) (8) Not only is the presence of acid... important but so is the severity of acidosis ... portant (Table III) (8) When pH is <7 10 the... two in three babies have an Apgar score of 0-3 ... in this situation immediate delivery is indicated

Type of acidosis

Classification of the type of acidosis is also ... portant but this information has not been gener... applied clinically because of the difficulty ... ing reliable measurement of low PO_2 levels ... laboratories

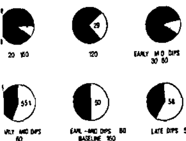
Asphyxial acidosis is defined when PO_2 is < ... mmHg and PCO_2 is >60 mmHg (9) Asphy... acidosis is usually severe and is often associa... with a fetus born in poor condition (Table IV) ... The various obstetric causes of asphyxia such ... abruptio placenta and cord complication are ... known

Metabolic acidosis is usually mild and the fetu... usually born in good condition (Table IV) Th...

Table VII *Fetal scalp blood measurements in the normal and growth retarded fetus*

Growth retardation	pH	PCO_2 mmHg	PO_2 mmHg	BE_p^{mEq}
None	7 35	46 8	23 4	−0 3
n	21	12	12	12
Moderate (3rd–10th percentile)	7 ?89	45 6	?? 1	−3 0
n	31	13	14	14
Severe (<3rd percentile)	7 ?23	54 5	20 9	−3 4*
n	13	8	8	8

Mann Whitney U test $p<0\ 05$



ig 2 FHR in relation to fetal scalp pH The percentage f cases with pH<7 25 is shown for each FHR group lips are synonymous with decelerations The incidence f fetal acidosis in the last two groups are significantly dif rent from the normal FHR group (11)

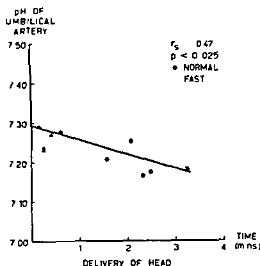


Fig 3 The pH of the umbilical artery was significantly lower with prolongation of the time taken for delivery of the head (10)

re various causes of metabolic acidosis Controlled ials using placebo and narcotic injections have hown that single standard dose injections of arcotic agents produce a mild metabolic acidosis in ie fetus (Table V) (1) Heroin has a more marked ffect than demerol pH changes more markedly ian shown when large or repeated doses of narcotics are given at short intervals

Fetal metabolic acidosis also occurs in hyperten ion either with or without proteinuria (Table VI) his metabolic acidosis may be due to the disease rocess itself the use of large and frequent doses of arcotic agents in this condition or possibly the se of other drugs Asphyxia the commonly held iechanism thought to influence the fetus in this isease is much less frequent and is only seen when ie fetus is born in poor condition Other causes of ietabolic acidosis are fetal growth retardation (Ta le VII) (12) amniotomy and maternal starvation 1) Also the latter two amniotomy and maternal tarvation are associated with maternal metabolic cidosis

Acidosis may be temporary and when this occurs does not markedly influence Apgar score (8) (Table VIII) A small series of proven cases of temporary acidosis where serial pH measurements were made had no very low Apgar scores The importance of temporary acidosis lies in the interpretation of mild to moderate degrees of acidosis in clinical management A pH between 7 15–7 25 may be wholly or partly due to temporary causes If pH is <7 15 a temporary cause is unlikely Temporary acidosis may occur at the time of amniotomy in the supine hypotensive syndrome following the use of narcotics or in association with transient bradycardia of the fetus perhaps resulting from cord compression

able VIII *Apgar score and temporary acidosis*

	Apgar score	
	0–3	4–10
H<7 0		
emporary	0	15
rsistent	15	31

=5 91 *P*<0 0?5

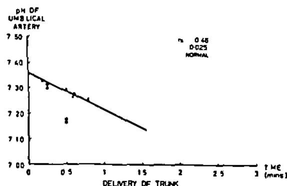


Fig 4 The pH of the umbilical artery was significantly lower with prolongation of the time taken for delivery of the trunk and limbs (10)

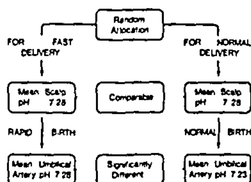


Fig 5 Diagrammatic scheme of controlled trial testing the effects of speeding birth Thirty patients were in the trial The two groups were matched for obstetric variables The umbilical artery blood pH in the fast group was significantly higher than in the normal group and that reported in six of seven studies of normal deliveries in other hospitals (10)

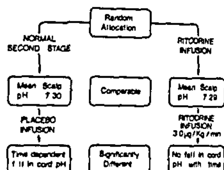


Fig 7 Diagrammatic scheme of controlled trial t effects of ritodrine (β mimetic) infusion in the stage Comparison of regression lines between (n=10) and ritodrine infusion (n=15) groups significant differences for umbilical venous pH PC PCO_2 and umbilical arterial PO_2 and PCO_2 Ri abolished the fetal asphyxia which normally occurred the late second stage (3)

Acidosis and other fetal diagnostic tests

As might be predicted acidosis is found more commonly when oestriol measurement is low (Fig 1) (2) When oestriol excretion is less than the tenth percentile on two consecutive occasions acidosis is subsequently found in 40% of cases whereas acidosis only occurs in 7% of cases when oestriol is normal In many instances oestriol production and excretion may be reduced without influencing fetal base status The combination of low oestriol production and acidosis at the time of induction labour usually warrants Caesarean section in experience

It is well known that abnormal FHR relates acidosis and in our studies the most strong cor lation is found between late deceleration acidosis approximately 60% (Fig 2) (11) By use computerized statistical analysis Hon and his c leagues (5) have shown a correlation between c tain FHR changes and acidosis in 70–80% of p tients However one would not expect an abso correlation between pH and FHR abnormalities a variety of reasons

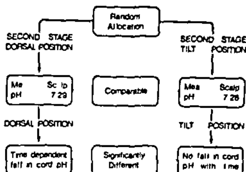
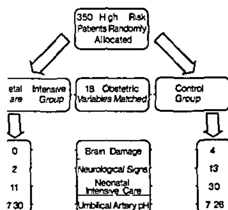


Fig 6 Diagrammatic scheme of controlled trial testing the effects of the dorsal and left tilt positions upon the fetus during the second stage Fall in pH (scalp capillary umbilical artery pH difference) was significant in dorsal but not left tilt position Dorsal r=0 68 p<0 01 n=20 Left tilt r=0 11 p ns n=20

Table IX *Neonates*

	Control	Intensive care
Apgar score		
0–3	6	4
4–6	19	24
7–10	150	147
Resuscitation at birth		
Nil	5	6
Routine	115	131
Intensive	55	37
Neonatal intensive care	30	11
Neurological signs and symptoms	13	2

* χ^2=8 95 p<0 001 χ^2=10 03 p<0 001



g 8 Diagrammatic scheme of controlled trial testing the fluence of fetal intensive care upon the high risk fetus he intensive care (n=175) and control (n=175) groups ere matched for 18 obstetric variables Significant differ nces were found in the neurological and biochemical atus of the newborn and the number requiring neonatal itensive care The four babies in the control group had evere brain damage which was still present six months ter birth

In clinical practice we use both FHR and scalp lood pH FHR is used routinely in high risk cases calp blood pH is done only when FHR abnormal y is present and no potentially reversible cause of HR abnormality is evident

irth asphyxia

calp pH has *helped in assessing other factors* hich may influence the fetus in labour Of practi al importance to the obstetrician is an understand ig of the asphyxia associated with birth The pH id PCO_2 of cord blood is related to the time taken or delivery of the head (Fig 3) and the time taken or delivery of the trunk (Fig 4) (10) Time limits for iese phases of birth have been suggested for our ospital This is particularly important in a teaching ospital where delay at birth might occur because ostetric attendants are inexperienced The basis of me limit was made from examining regression ies and estimating the times over which pH shifts l unit The head delivery time should not exceed vo minutes and the trunk delivery time 45 sec ids

The birth acidosis and asphyxia may be de eased by speeding delivery (Fig 5) (10) avoiding olonged use of the dorsal position in the second

77 866

Table X *Neonatal diagnoses*

Diagnoses	Control	Intensive care
Brain damage	4	–
Perinatal hypoxia	3	1
Cerebral hypoxia/irritation	2	–
Apnea/cyanotic attacks	2	–
Tachypnea	2	–
Uncertain	2	1
Hypoglycemia	1	–

stage (Fig 6) (4) or by the use of ritodrine (Fig 7) (3)

There is a view that mild asphyxia may be a physiological change associated with birth which is important in the adaptation of the fetus to extra uterine life However we found no evidence to support this hypothesis as the fetus suffering the mild asphyxia of birth showed no evidence of clini cal benefit over those suffering none

An excess of birth asphyxia should be avoided by placing time limits on the birth process If the fetus is thought already to be at risk the extent of birth asphyxia may be reduced by expediting delivery

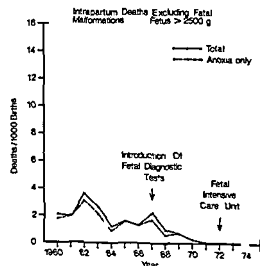


Fig 9 The reduction of *intrapartum anoxic stillbirths* over ten years at the Queen Victoria Hospital r=0 89 p<0 001 Comparison of intrapartum deaths before and after 1967 showed a significant difference χ^2=25 39 p<0 001 Although a number of factors are involved in the decline in intrapartum stillbirth rate the introduction of fetal diagnostic tests is thought also to have contributed to this change

and avoiding prolonged positioning of the patient in the dorsal position

Effect of monitoring on fetal condition

The use of scalp sampling for routine fetal monitoring has been associated with a lower perinatal mortality in several centres Used in conjunction with FHR monitoring a carefully controlled trial in our own institute demonstrated that monitoring and scalp sampling was associated with improved neurological and biochemical status of the newborn and less need for neonatal intensive care (Fig 8) (Tables IX X) (This trial will be published in more detail subsequently) The two groups were matched for 18 obstetric variables The improved status of the newborn in the intensive care group was thought to be due to the more accurate diagnosis of fetal distress rather than other factors involved in the trial Caesarean section and forceps delivery were not more common in the intensive care group

The use of FHR monitoring and scalp sampling may have contributed to the decline in intrapartum anoxic stillbirth in our own institution (Fig 9) Fetuses >2 500 g no longer die in labour

ACKNOWLEDGEMENTS

I wish to acknowledge the help of the Obstetric and Nursing Staff of the Queen Victoria Hospital and the members of the University Department who have helped in these studies

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Submitted for publication Feb 27 1977

Carl Wood
Department of Obstetrics and Gynaecology
Monash University
Queen Victoria Memorial Hospital
Melbourne Victoria
Australia

Acta Obstet Gynecol Scand 57 19–24 1978

?ERINATAL MORTALITY IN HYPERTENSIVE PREGNANT PATIENTS ITS REDUCTION IN A DEVEI OPING COUNTRY

Bussamara Neme and Ivo Behle

From the Obstetric Clinic of the Sao Paulo University Medical School Sao Paulo Bra il

ırıous authors (2 28 48) have called our attention the great dısparıty existıng ın the curves of ma rnal and perınatal mortalıty They have pointed t that the latter has decreased relatıvely lıttle ıce 1945

Among other reasons this was due to limited terest in studying the physiology of the human tus (1) This has changed within the last ten years ›wever Because of studies of amniotic fluid to maternal hormones and the application of en ımology biochemistry biophysics and electronics the study of biological phenomena knowledge ›out the fetus has been considerably increased

Hypertension is one of the clinical conditions hich concerns most obstetricians It stands out ɛcause of its high incidence (8 11 18 25 47) and ɛrious fetal prognosis (2 7 9 12 15 22 23 25 32 ‡ 46) *Its manifestation and intensity are particu* rly important in developing countries where pre atal assistance and methods for assessing fetal ɾell being and maturity are limited

Considering these special conditions of develop- ıg nations (within which we are included) we ɛcided to see how far simple tests easily applied nd interpreted could reduce fetal loss These tests ould be used to calculate the timing of opportune ıerapeutic preterm delivery in hypertensive regnant patients

MATERIAL AND METHODS

he study consisted of 596 hypertensive pregnant patients ›spitalized in the Obstetric Clinic of Sao Paulo Uni rsity Medical School and in the Casa Maternal e da ıfância

All the patients were in the third trimester of pregnancy ıd their arterial pressure was always higher than 14×9 mmHg They were all under the care of a team of doctors charged especially with the treatment of the hypertensive pregnant patients This consisted fundamentally of hospitalized in the Obstetric Clinic of Sao Paulo Universi ty lateral decubitus low sodium low carbohydrate low fat high protein diet plenty of water sedatives hypo- tensive drugs (when the pressure was over 18×11 mmHg) psychotherapy and diuretics

These 596 patients were divided into 4 groups according to the methods employed in order to monitor the well being and maturity of the fetus

Group I (1962–1967) 214 patients in which fetal welfare and maturity were evaluated clinically only fetal heart rate active fetal movements cessation of uterine growth date of last menstruation height and circumference of the uterus reduction in volume of the amniotic fluid etc

Group II (1968–197') 181 pregnant patients in which fetal well being was monitored by amnioscopy and amnio- centesis (signs of meconium) Maturity was estimated by creatinine analysis cytology (orange cells) of the amniotic fluid and by Clements test (estimation of fetal pulmonary surfactants)

Group III (1973) 90 pregnant patients in which in addi tion to the tests mentioned in Group II fetal well being was also evaluated by exercise (4) and tolerance to oxyto- cin (10 30) tests using electronic equipment

Group IV (1974–1975) 111 pregnant patients in which fetal well being and maturity were evaluated by the same tests used in Group III except that in place of electronic monitoring for the stress tests we used only simple clinical

Table I *Perinatal mortality (1975)*

Groups	Mortality					
	Stillbirth		Neo-natal		Perinatal	
	No	%	No	%	No	%
I 214 cases (1962–67)	?3	10 7	16	39	7 4	18 2
II 181 cases (1968–7')	5	2 7	9	14	4 9	7 7
III 90 cases (1973)	0	0	1	1	1 1	1 1
IV 111 cases (1974–75)	?	1 8	2	4	1 8	3 6

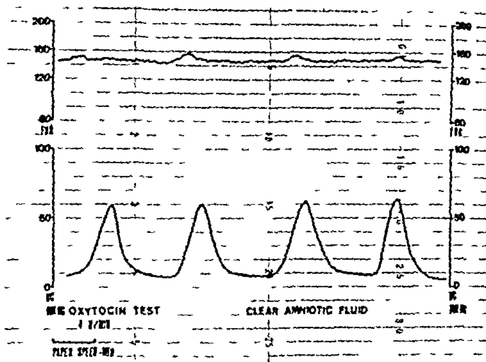


Fig 1 Negative oxytocin test

methods In these cases fetal heart rate was monitored by Doptone and uterine activity by manual palpation

Tests of fetal health were performed from the twenty eighth week Whenever possible therapeutic preterm delivery was postponed to the thirty fourth week or if possible to the thirty sixth week of pregnancy

A Saling (36) cannula and a Rodrigues Lima (33) acrilic amnioscope were used for the amnioscopy Amniocentesis was always trans abdominal umbilical and supra pubic The presence of meconium in the amniotic fluid was always considered to be a sign of fetal distress justifying immediate (meconium

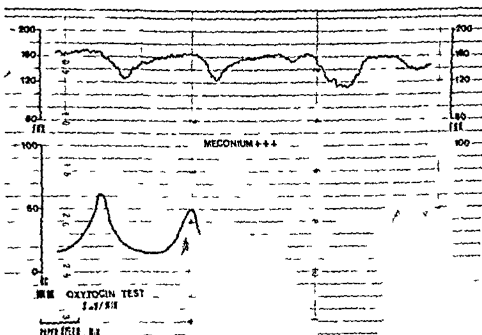
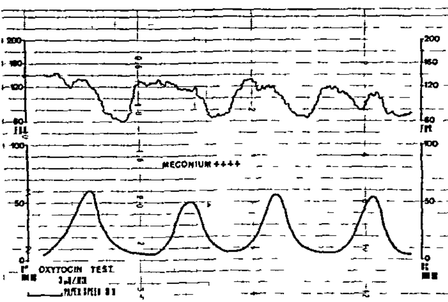
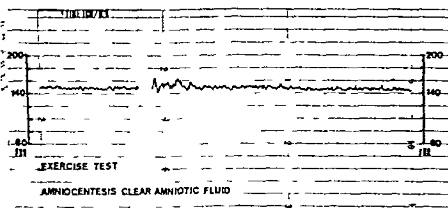


Fig 2 Positive oxytocin test



g 3 Positive oxytocin test



g 4 Negative exercise test.

able II *Perinatal mortality and newborn weights*

	Newborn weights						
	–1 500 g		1 501–2 500 g		2 501 g		Perinatal mortality (%)
roups	No	%	No	%	No	%	
I (276 newborn)	14	69	6 1	30.5	143	63 3	18 2
I (184 newborn)	5	[illegible]	2 7	28 3	125	67 9	7 7
I (91 newborn)	5	50	5.5	54 9	36	39 5	1 1
(111 newborn)	4	27	3 6	24 3	80	[illegible]	3 6

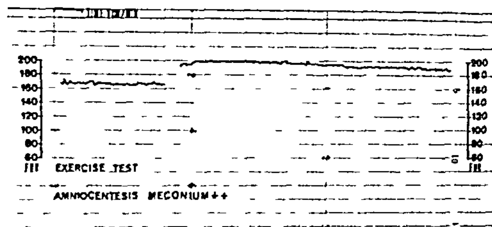


Fig 5 Positive (tachycardia) exercise test.

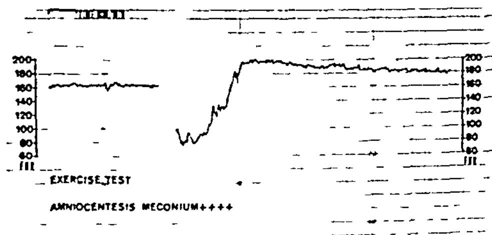


Fig 6 Positive (bradycardia) exercise test

*) or slightly delayed (meconium and) preterm therapeutic delivery

Classical methods (10 30) and interpretation were used for the oxytocin tolerance tests

A personal technique (4 27) was used for the exercise tests The patients were asked to sit up many times from the horizontal decubitus position until they felt tired presence of fetal tachycardia and especially bradycardia after this effort were felt to be manifest of a fetus already compromised in utero

If the exercise and oxytocin tests were repeated simultaneously positive then therapeutic preterm very was indicated even in the absence of meconium the amniotic fluid Under these circumstances ces section was the procedure of choice

Table III *Delivery and perinatal mortality*

Groups	Delivery Vaginal No	%	Abdominal No	%	Perinatal mortality (%)
I (224)	184	82 1	40	17 9	18 2
II (181)	86	47 8	95	52 2	7 7
III (90)	42	46 7	48	53 3	1 1
IV (111)	48	43 3	63	56 7	3 6

RESULTS

Tables I II and III show data pertinent to per mortality found in the four groups of pregn tients and the relationship between the weight new born and the type of delivery

Figures 1–6 show examples of amniocentesis ercise and tolerance to oxytocin tests perform the same patients

DISCUSSION

The results in Table I show that perinatal mortality in hypertensive pregnant patients was reduced from 18 2% (group I) to 7 7% (group II) by using the amnioscope and amniocentesis

This reduction was even more pronounced (1 1%) when in addition to those tests fetal well being was evaluated by monitored maternal exercise and oxytocin tolerance tests (group III)

Since hospital facilities in developing countries usually do not include electronic methods we tried to use clinical methods instead

This resulted in an increased perinatal mortality from 1 1% to 3 6% (group IV)

However we want to point out that this figure (3 6%) is much lower than that for patients in group I (18 2%) in which more accurate tests of fetal well being and maturity were omitted

Table II shows that the excellent perinatal results obtained in group III were not related to the lower incidence of prematurity on the contrary it was in this group that the incidence of infants weighing less than 2 500 grams was greatest (60 4%) It appeared to be due to the greater accuracy of the electronic methods used in the study which detected the compromised fetus before the excretion of meconium occurred so that even earlier intervention by therapeutic preterm delivery (27 42) was employed

Finally Table III shows that the incidence of cesarean section was increased in groups II III and IV compared to those in group I This fact is related to the earlier and frequent finding of chronic fetal distress when amnioscopy and amniocentesis (group II) and the maternal exercise and tolerance to oxytocin tests were used (groups III and IV) and also to the aggravated perinatal risk when vaginal delivery is performed under these circumstances (30 31 40)

These results are supported by the observations of various authors (5 17 19 35 37 38 43) The latter show the relationship of chronic fetal distress to the presence of meconium in the amniotic fluid and emphasize the merits of the amnioscope (7) and amniocentesis (3 20 21 36) for its identification

The high incidence of changes in fetal heart rate (tachycardia and especially bradycardia) after maternal exercise test and after normal uterine contractions (13 14 16 24 27 29 39 41) in hypertensive pregnant patients (4 26 45) was used for the early identification of changes in fetal well being in these cases even in the absence of meconium in the amniotic fluid (27 42)

Finally one must take into account that perinatal mortality in high risk pregnant patients justifies preterm therapeutic delivery and a more liberal indication for delivery by cesarean section after the 34th week (44 49)

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Submitted for publication Nov 22 1976

Bussâmara Neme
Dept of Obstetrics and Gynecology
University of San Paulo
Brazil

Acta Obstet Gynecol Scand 57 25–33 1978

PREMATURE LABOR TREATMENT WITH RITODRINE IN MULTIPLE PREGNANCY WITH THREE OR MORE FETUSES

Joseph Bieniarz Niranjana Shah W Paul Dmowski
Ramaa Rao and Antonio Scommegna

From the Laboratory of Uterine Physiology Department of Obstetrics and Gynecology Michael Reese Hospital and Medical Center and the Pritzker School of Medicine of the University of Chicago Chicago USA

bstract Modern treatment for anovulatory infertility in the incidence of multiple pregnancies with three or ore fetuses and predisposes to prematurity with high ırinatal mortality and morbidity Premature labor was ıccessfully treated in four multifetal pregnancies with todrine hydrochloride a beta mimetic drug relaxing the terus Another patient misdiagnosed as false labor was ot treated and lost three out of four premature babies ieta mimetic treatment is indicated in multiple preg ancies even in false labor or when painless progress in ervical dilatation is observed to avoid asymptomatic rogression into true labor In contrast to singleton preg ancies advanced labor with more than four centimeters ervical dilatation should not preclude good chances for uccessful treatment Persistence in treatment and re ıeated use of the most effective intravenous route com ıned with oral ritodrine administration is needed because of marked tendency to recurrences of premature labor Progressive increase in the dose of oral ritodrine may be ndicated by decrease in therapeutic response Maternal achycardia should be considered as an index of patient esponsiveness to the beta mimetic treatment The thera y is most successful when the patient is hospitalized from he first episode of treatment until at least the 37th week of pregnancy This is probably less expensive than pro onged hospitalization of several prematures in an inten ive care nursery

The spontaneous occurrence of multiple pregnancy with three or more fetuses is rare once in 9800 births for triplets (1) once on 677000 births for quadruplets and once in 8–20 million births for quintuplets (2) Recently the incidence of multifetal pregnancies increased dramatically due to treat ment of anovulatory infertility by agents inducing multiple ovulations Human Menopausal Gonado tropin (HMG) Human Pituitary Gonadotropins (HPG) Clomiphene Citrate (Clomid) and Human Chorionic Gonadotropin (HCG)

The incidence of multiple pregnancy is in the range of 8 to 10% in Clomid treated women (3) while among those treated with exogenous gonado tropins it is as high as 20 to 40% (4) Considering that almost half of the patients in the latter group carry three or more fetuses (5) and that a significant number of these multifetal pregnancies terminate in abortion or premature labor with very high peri natal loss the fertility drugs have been a mixed blessing to many infertile women

Prematurity is the single most important cause of the high perinatal morbidity and mortality in multi fetal pregnancy With the rising number of fetuses the degree and incidence of prematurity increase as well Prematurity occurs in 54% of twins as com pared to 9% of singletons (6) The perinatal mortal ity rates expressed as the number of stillbirths and neonatal deaths per 1000 total births of single twin triplet and quadruplet gestations were respec tively 39 152 309 and 509 (7) The mean length of a twin pregnancy is 37 weeks (8) it is 35 weeks for triplets 33 weeks for quadruplets (1) and 30 weeks for quintuplets (2) The progressively shorter preg nancy and earlier onset of labor were attributed to the early uterine distension (1) The amount of distension that the uterus will tolerate was found greater in multiparas than in primigravidas whose tendency to prematurity is greater (1)

Known relaxants of the myometrial cell e g beta mimetic drugs could increase the tolerance of the uterus to distension and delay the onset of labor Ritodrine hydrochloride a new beta mimetic drug allegedly has a selective action on the myo metrium without producing marked arterial hypo tension or tachycardia (9 10 11)

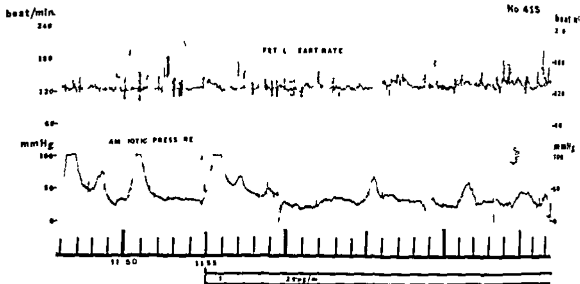


Fig 1 S K G1 P0 in premature labor 3 nd week of a quadruplet pregnancy Marked sensitivity to beta mimetic drugs is indicated by a rapid inhibition of uterine contractions after onset of low rate intravenous ritodrine infusion The uterus relaxed completely in two hours

The aim of this study was to test the effectiveness of ritodrine in delaying the onset of labor in multi fetal pregnancies

MATERIAL AND METHODS

Ritodrine hydrochloride was graciously supplied by Philips Duphar Laboratories Weesp Holland Treatment was begun with an intravenous infusion 50 mg/200 ml saline at a very low rate of 50 µg/min which was then lly increased by 50 µg/min every 10 min not to 400 µg/min until adequate uterine relaxation or acceptable side effects occurred (e g maternal tachy over 130/min or hypotension <90/50 mmHg) The infusion rate was then reduced until side effects disappeared

Uterine contractility and fetal heart rate were recorded on a Hewlett Packard cardiotocograph Model 8070A Maternal heart rate and blood pressure were checked and tabulated each 10 min until the effective ritodrine dose was established and the uterus was relaxed There after all these signs were checked every two to hours

Depending on the established sensitivity to ritodr infusion treatment was maintained for 1? ?4 hours was followed by oral treatment with 10–30 mg (1 3 tab 4–8 times daily The patient was confined to bed du infusion and for the first day of oral treatment Th after limited activity was allowed but the patient mained hospitalized at least until the end of the 36th w of pregnancy

CASE STUDIES

Three white women with longstanding primary infert have been treated with injections of HMG for 18 to days (1 amp = 75 IU of FSH and 75 IU of LH) until plas estradiol has risen to 400–1 000 pg/ml or urinary estrog to 100–150 µg/day At that time an injection of H 10 000 IU was administered Two black women G2 P1 the other G9 P8 conceived spontaneously with any medication Multiple pregnancy was suspected

Table I *Premature labor recurrences in a ritodrine treated quadruplet pregnancy (S K G1 P0)*

No	Gestation weeks	Cervix Dilat	Effac %	Station	Treatment I V (µg/min)	Duration (h)	Oral (mg q h)	Duration
1	32	1 5→2	30→60	−2→−1	25	24	10 3	20 h
2	32	2	50	−2	50	24	10 2	11 h
3	32 5	1 5	50	−?	150	18	?0 3	16 d
4	35	2	80	0	Discontinued because of complicating pre-eclampsia			

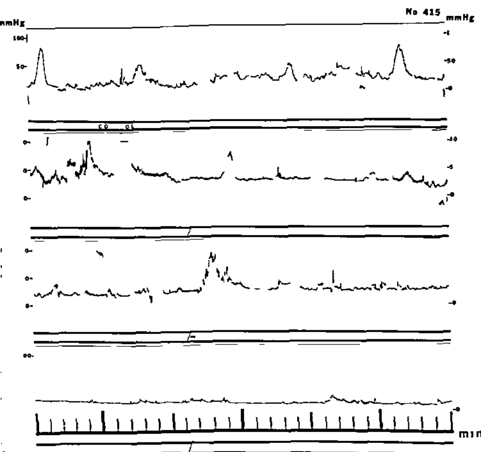


Fig 2 The same patient as in Fig 1 during the third recurrence of premature labor three days later A higher rate of ntodrine infusion was needed to relax the uterus This patient presented three recurrences of premature labor while on oral treatment controlled by intravenous ntodrine infusion

because of rapid increase in uterine size incompatible with gestational age The diagnosis was confirmed by ultrasound in three women during early pregnancy and by X ray at 30 weeks in the other two women All women were treated by bedrest with very limited activity (bathroom privileges)

WOMEN TREATED FOR INFERTILITY

Quadruplet pregnancy

S K a 27 year-old white woman was hospitalized at the 32nd week of her pregnancy because of labor pains progressively increasing in frequency and intensity for the

Table II *Premature labor recurrences in a ntodrine treated triplet pregnancy (J S GI P0)*

No	Gestation weeks	Cervix			Treatment			
		Dilat	Effac %	Station	I V (µg/min)	Duration (h)	Oral (mg q h)	Duration (days)
1	31	0→Ft	0→50	−3	50–300–200	13	20 6	2 5
2	31 5	0	30	−3	50–300– 00	8 +	10 3	17
3	34	0	70	−2	50–200–100	15 +	10 4	3
3	36 5	1	80	0	50–?00	18 +	10 3	10
5	36	Ft	80	0			10 2	1
	36	Ft	80	0			10 3	7
	37	Ft	80	0	Treatment stopped			7
5	38	3	90	+?	Onset of labor			



Fig 3 J S G1 P0 premature labor at the 31st week Flat plate of abdomen shows three fetuses On ritodrine treatment pregnancy was continued until term

preceeding 12 hours The diagnosis of true premature labor was confirmed by a bloody show and progress in cervical dilation in one hour from 1 5 to 2 cm effacement from 30 to 60% and descent from station −2 to −1 (Table I)

Ritodrine was started with half the usual intravenous infusion rate 25 µg/min which was sufficient to cause a complete uterine relaxation in two hours (Fig 1) After 24 hours infusion was stopped and oral treatment was started with one tablet of 10 mg every 3 hours

During 20 hours on oral treatment the maternal pulse rate slowed down from 100 to 80 beats/min and uterine contractions reappeared A second intravenous infusion at 50 µg/min was begun and discontinued after 24 hours This was followed by oral treatment 10 mg every tw hours (Table I) After 11 hours the contractions re peared and for a third time intravenous infusion w restarted and continued at a higher rate of 150 µg for 18 hours Again uterine contractions disappea within 1 5 hours from onset of infusion (Fig 2)

Oral treatment was increased to 20 mg every thr hours This dose accelerated maternal pulse to 90- beats/min and maintained the uterus relaxed until t 35th week of pregnancy when labor contra tions sta again Because of signs of pre eclampsia BP 150 mmHg proteinuria ++ and weight gain no attempt h been made to stop labor Seven hours later the patie delivered under light general anesthesia four infa

able III *Premature labor recurrences in a spontaneous triplet pregnancy (M K G2 P1)*

No	Gestation weeks	Cervix Dilat	Effac %	Station	Treatment I V (µg/min)	Duration (h)	Oral (mg q h)	Duration (days)
	32	4→6	60→80	−4→−1	200–300 +50 g ethanol 1 h	24	20 3	2
	32 5	7	70	0	+50 g ethanol 3 h		30 3	7
	33 5	7	90	+1	400–300	24	40 3	11
	35	9	100	+2	RBOW Onset of labor			

uring 40 min 1st male—vertex by outlet forceps Apgar ore 7/10 weight 1 575 g 2nd female—by internal podalic rsion and extraction from transverse lie Apgar score 9 weight 1 800 g 3rd male—with a floating head by in rnal podalic version and breech extraction Apgar score 9 weight 1 800 g 4th male—by breech extraction Apgar ore 1/9 weight 1 800 g

The gestational age of the newborns assessed by Dubowitz score was 35 weeks The postpartum course was un ventful and the patient was discharged from the hospital days later All four infants progressed well in special are nursery and were discharged after three weeks when eir weight reached 2 000 g

iplet pregnancy (Fig 3)

S a white 27 year-old G1 P0 was hospitalized at 31 eeks of gestation with painful regular contractions of creasing frequency and intensity True premature labor as recognised by progress from a long closed and osterior cervix to a fingertip open and 50% effaced uring one hour Intravenous administration of ritodrine as started at increasing rates from 50 to 300 µg/min hich had to be reduced to 200 µg/min due to marked aternal pulse acceleration from 90 to 144/min Uterine ontractility was completely inhibited in 2 5 hours the in sion continued 13 hours On oral treatment 20 mg every hours the patient was gradually mobilized during 2 5 ays Similarly as in quadruplet pregnancy there were veral recurrences of premature labor when the patient as on oral treatment. They are summarized in Table II

Starting with the second recurrence intravenous ritodrine infusion was combined with oral treatment which as maintained throughout the infusion period This com ned administration marked on Table II by + between travenous and oral treatment was well tolerated except ir transient palpitations immediately after ritodrine in stion

Urinary estriol excretion was high 30 7 mg/24 hours 32 weeks and progressively increased to 62 4 mg/24 ours at 38 weeks The biparietal diameter measured at o weeks intervals showed values consistently lower by weeks than expected from gestational age but increas g progressively Amniocentesis at 36 weeks and 38 eeks has shown surprisingly low L/S ratios 1 0 and 1 4 spectively while creatinine concentration and per ntage of orange cells suggested good maturity 1 8 mg /9 mg as well as 10% and 18% respectively Routine boratory evaluation presented normal values except for elevated uric acid levels (8 3 mg%) at 38 weeks No signs of pre eclampsia were observed

At 37 weeks oral treatment has been discontinued At the 38th week 8 weeks from onset of treatment labor started (Table II) and progressed smoothly to a spon taneous delivery of three infants in 28 min each from vertex presentation under pudendal block anesthesia 1st male—Apgar score 9/10 weight 2 290 g 2nd female—Apgar score 8/10 weight 2300 g 3rd female—Apgar score 7/10 weight 2 170 g

The Dubovitz score of the newborns was 37 to 38 weeks The neonatal course was without complications

Quintuplet pregnancy (premature labor not treated with ritodrine)

E I a 26-year-old white woman was hospitalized at the 27th week of pregnancy with a term size uterus because of a mucous and watery discharge without pains Negative nitrazine and fern tests excluded ruptured bag of water No uterine contractions were recorded cervix was 1.5 cm dilated and 50% effaced and did not progress during 48 hours The woman has not been treated with ritodrine because the diagnosis of true premature labor could not be established She has been alerted to report immediately uterine contractions The patient disregarded mild discomfort until pains became strong and membranes ruptured The cervix was found six centimeters dilated 50% effaced station +2 She delivered within one and a half hours under pudendal anesthesia 1st female—vertex NSVD Apgar score 3/7 945 g 2nd amorph us monster—of the same amniotic sac Apgar score 0/0 15? g 3rd male—spontaneous breech Apgar score 4/6 845 g 4th male—assisted breech Apgar score 3/6 960 g 5th male—breech extraction Apgar score 3/6 900 g

The condition of the first and fifth baby was poor that of the third and fourth was fair All four developed respiratory distress syndrome with repeated periods of apnea and bradycardia treated with continuous positive airway pressure (CPAP) and oxygen resuscitation Only the first baby survived treated with Ampicillin Kanamycin and blood transfusions The baby was discharged after 70 days of hospitalization in good condition weighing 1 900 g

Spontaneous triplet pregnancies conceived without fertility treatment

M K a 21 year-old black G2 P1 was hospitalized at the 32nd week of pregnancy because of premature labor

recognized by rapid progress in cervical dilatation from 4 to 6 cm effacement from 60–80% and descent from −4 to −1 station in one hour although no labor pains were felt by the patient Uterine contractions of increasing frequency were recorded five to two minutes apart Ritodrine I V infusion was started and increased to 300 μg/min spacing uterine contractions 10–12 min apart Complete uterine relaxation was attained with the additional ethanol treatment 50 g in 1000 cc 1/2 dextrose 1/? N saline infused in one hour and repeated during the following three hours (Table III)

No further progress in labor has been observed and the combined intravenous infusion has been discontinued after 24 hours Oral ritodrine 20 mg every three hours has been started and had to be increased two days later to 30 mg every three hours (Table III) because maternal pulse slowed down from 1?0 to 80/min

No signs of pre-eclampsia have been observed Urinary 24 hour estriol excretion increased from 22 2 to 39 8 mg/24 hours between 3?nd and 33rd 1/2 weeks At that time regular contractions every 3–4 min started again cervix was found 7 cm dilated and 90% effaced with the head engaged +1 (Table III) A repeat intravenous ritodrine infusion had to be increased to 400 μg/min to inhibit uterine contractility again It was reduced to 300 μg/min and was maintained during 24 hours but the cervix remained 7 cm dilated The patient was kept in absolute bedrest in Trendelenburg position Difficulties in complete bladder evacuation forced us to grant the patient bathroom privileges

At the 35th week of pregnancy the BOW ruptured with 9 cm dilatation 100% effacement and station +2 The patient delivered in 1 hour 51 min under pudendal anesthesia with a mediolateral episiotomy 1st male—spontaneous vertex Apgar score 6/7 weight 2220 g 2nd male—spontaneous breech Apgar score 6/7 weight 2140 g 3rd male—spontaneous vertex Apgar score 4/6 weight 1880 g

All babies were discharged 9 days later in good condi n

M H was a 46 year-old G9 P8 with triplets diagnosed by ultrasound at the 23rd week of pregnancy (Fig 4a b) She was hospitalized at 33 weeks in premature labor In spite of ethanol treatment the cervix dilated from 1 to 1 5 cm effaced from 30 to 60% and the station changed from −3 to −1 Ritodrine infusion 250 μg/min stopped further progress of labor and was substituted after 24 hours by oral ritodrine 20 mg q 4 hours The dose had to be increased to 30 mg q 3 hours at the 35th week because the maternal heart rate tended to descend from 110 to 80 beats/min This treatment was well tolerated and continued until the 38th week when amniocentesis confirmed fetal maturity L/S ratio ? 3 orange cells 20% and creatinine 1 8 mg/% Ritodrine treatment was stopped two days later membranes ruptured and labor started Three female newborns were delivered spontaneously in 2 hours and 15 min from vertex presentations with Apgar score of 9/9 each and weights of 1830 g 2380 g and 2385 g respectively Except for transient hypoglycemia of the first small gestational age infant the neonatal course of these near term babies was uneventful

COMMENTS

Ritodrine hydrochloride treatment has been cessful in delaying the onset of true premature in four multifetal pregnancies with salvage of infants In another woman who did not present nite signs of labor at the 27th week we missed right time for early treatment with loss of three of four babies In the quadruplet pregnancy began at 31 weeks of gestation however the ery was postponed with ritodrine treatment un 35th week It is conceivable that even further of labor could have been achieved in this However we elected to discontinue treatme cause of complicating pre eclampsia In three pregnancies labor began at the 31st week livery was postponed until term in two and the 35th week in one There was no perinatal tality in ritodrine treated patients although a 31% in triplets and 51 percent in quadruplets be expected (7) Delivery occurred 2 to 3 w later than could be anticipated on the basis number of carried fetuses (1)

One major problem in assessing the effica treatment in premature labor was the diffi distinguishing between true and false labor If labors were included into the study group it w bias the results because uterine contractions off even without treatment In singleton nancies a basic requirement for including a into ritodrine treatment is a confirmed p cervical effacement dilatation and descent of presenting part (9) generally considered as p a true labor On the other hand in multifetal nancies it is much more difficult to distingui tween true and false labor because cervical tion effacement and descent of the presenting may be observed long before onset of labor marked uterine distension The genital tract so

Fig 4a M H G9 P8 23rd week of pregnancy tudinal midline ultrasound scan reveals two fetal (1 & ?) *S*=Symphysis *U*=Umbilicus *P*=Place Amniotic fluid Polyhydramnios is present

Fig 4b Longitudinal ultrasound scan 3 cm to the the midline in the same woman visualizes a third f in breech footling presentation (*h*=fetal heart) weeks of pregnancy premature labor was stopped ritodrine treatment and pregnancy continued until From A Cadkin and M Motew Clinical Atlas of Scale Ultrasonography in Obstetrics Charles Publ Springfield (with authors & publishers permi (In press)


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2

pared is predisposed to an almost asymptomatic progress into an irreversible active phase of labor as in our case of quintuplets and in one of our triplets (M K)

In multiple pregnancy it is safer to treat a false premature labor unnecessarily than to overlook an asymptomatic progress of labor risking early prematurity with its high perinatal mortality and morbidity This is especially important in women who conceived after longstanding infertility, and who are desperate to have living and healthy children

The observations collected in the second triplet pregnancy (M K) suggest that criteria of failed treatment accepted for singleton pregnancy i e cervical dilatation over 4 cm and marked effacement 80% are not valid in multiple pregnancies The marked uterine distension makes the diagnosis of labor more difficult On the other hand it makes possible a prolonged delay of an advanced labor even though uterine contractions are not completely inhibited Absolute bedrest in Trendelenburg position indicated in these cases may be difficult to enforce because of the breathing difficulties and voiding discomfort

A prolonged hospitalization almost until term is indicated by the marked tendency to recurrences necessitating immediate repeating of intravenous treatment This can be assured only if the patient is hospitalized It is less expensive and more rewarding to keep a mother hospitalized for several weeks than to treat several prematures in an intensive care nursery for prolonged periods of time

Combined intravenous and oral ritodrine administration seemed to be most successful in inhibiting recurrent uterine contractility (see Table II) Close monitoring of maternal pulse on oral treatment helped to reduce the incidence of recurrences The initial marked response to ritodrine decreases with time necessitating progressively increasing doses to maintain the uterus relaxed Maternal heart rate is a good indicator of the changing sensitivity to beta mimetic drugs Whenever the maternal pulse decreases below 80/min a recurrence of premature labor may be expected By increasing the oral ritodrine dose a positive chronotropic effect takes place with tachycardia of 90–120/min and generally efficient inhibition of the uterine contractility

Finally alcohol a known inhibitor of oxytocin release may be combined with the relaxing effect of beta mimetic drugs on the myometrial cell in a combined multi target approach for prevention and treatment of premature labor (17)

Preparations for multiple delivery consist in organizing well in advance an alert emergency team available at any time It consists of obstetricians neonatologists (one for each expected newborn) anesthesiologists and nurses An adequate obstetrical instrumentation warmers resuscitation equipment and blood must be ensured

The conduct of labor aims at reducing the mechanical stress on the premature baby s head during its passage through the genital tract maintenance of an intact bag of water until full dilatation is reached application of outlet forceps and episiotomy Prevention of postpartum hemorrhage is indicated by manual intrauterine exploration checking of cervical and vaginal lesions and judicious use of oxytocics If labor does not progress smoothly or complicated obstetrical operations are envisioned delivery by cesarean section is advisable

Although these preliminary observations need further confirmation on a larger material they are of basic interest in view of increasing incidence of multifetal pregnancy in modern obstetrics and the limited modalities of treatment currently available (5)

ACKNOWLEDGEMENTS

This study was supported by N V Philips D… Weesp The Netherlands and Michael Reese Medical Research Institute Council

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Submitted for publication Feb 27 1977

Joseph Bieniarz
Department of Obstetrics and Gynecology
Michael Reese Medical Center
Chicago Illinois 60616
USA



Acta Obstet Gynecol Scand 57 35–40 1978

THE THERMOGENIC ACTIVITY OF EXOGENOUS E AND F PROSTAGLANDINS IN HUMANS

James R Dingfelder and William E Brenner

From the Department of Obstetrics and Gynecology University of North Carolina Medical School Chapel Hill North Carolina 27514 USA

basic understanding of the physiologic effects of the ·ostaglandins on the human reproductive system has ;en one of the diverse scientific interests of Professor xel Ingelman Sundberg (19) Although the obvious inical utility of these ubiqitous compounds directed arly attention to their therapeutic aspects more recently iere has been renewed interest in the basic physiologic iechanisms of the prostaglandins in reproductive medi ine Undoubtedly the work of Dr Ingelman Sundberg as stimulated many of his colleagues students and fel ›w scientists to pursue such basic studies in greater de uls

'he reporting of thermal (thermogenic) side effects fter administration of prostaglandin to humans has ceived scant mention in the general literature lthough pyrexia of various degrees is occasional / mentioned it has usually been considered as a ossible indicator of morbidity presumably sec ndary to endometritis or other infection There ave been few reports on the thermogenic effects f exogenous prostaglandin of various types given y several routes in human subjects Since prosta landins appear to be intimately involved in physio ›gical and pathological temperature regulation resumably both on a central nervous system and peripheral circulatory agents a closer inspection [temperature changes after prostaglandin ad unistration appears warranted

MATERIALS AND METHODS

tensive observations were made on 194 subjects be een 18 and 4? years of age and 8 and 2? menstrual eeks gestation who were aborted in the Clinical Re arch Unit of North Carolina Memorial Hospital Chapel ill North Carolina (USA) Particular attention was di cted to the following clinical observations

1 Hourly oral temperature
? Presence of visible shivering
3 Presence of endometritis and other infection
4 Subjective feelings of cold or hot

All subjects received intramuscular prostaglandin in jections according to the dose schedules outlined in Table I Since previously reported (4) experience had mentioned possible thermogenic side effects prophylactic medica tions were given in various combinations to certain sub-groups to attenuate these and other side effects as out lined in Table II Only group E3c subjects who had re ceived the PGE2 analogue also received aspirin No sub-jects who had been treated with PGF2a analogue received aspirin since only the E analogue had been reported to have been associated with pyrexia

15(S) 15 methyl prostaglandin E? methyl ester in an original concentration of 2 mg per milliliter was diluted with normal saline to a concentration of 15 µg per milli liter while 15(S) 15 methyl PGF2a Tham salt was given in

Table I *Groupings of patients receiving various doses of 15 methyl prostaglandin E2 and F2a ana logues*

Group	Sub-jects	Dosage	Medications
I *15 (S)-15 methyl PGE2 methyl ester (I M)*			
E1	20	5 µg q 4 h	–
E2	10	10 µg q 8 h	–
E3a	31	10 µg q 4 h	–
E3b	36	10 µg q 4 h	10 mg diazepam I M I h be fore induction
E3c	32	10 µg q 4 h	Concomitant medications (see Table II)
E4	5	25–50 µg q 8 h	–
II *15(S)-15 methyl PGF2a methyl ester (I M)*			
F1a	70	250 µg q 2 h	–
F1b	40	250 µg q 2 h and cervical laminaria	Concomitant medications (see Table II)

Table II *Concomitant prophylactic medications given to selected subgroups of patients*

I *Group E3c*

A Prochlorperazine
 1 10 mg I M one hour before induction
 2 25 mg rectal suppository every six hours after induction until abortion

B Lomotil (Searle brand of diphenoxylate HCl 2 5 mg and atropine sulfate 0 025 mg per tablet)
 1 4 tablets one hour before induction
 2 2 tablets every *four hours* after induction until abortion

C Acetylsalicylic acid
 1 1 3 g p o one hour before induction
 2 300 g rectal suppository every four hours after induction until abortion

II *Group F1b*

A Prochlorperazine—same as above
B Lomotil—same as above
C Acetylsalicylic—*none given*

one milliliter undiluted doses Administration was by deep *gluteal muscle injection* These were no significant differences in the ages *parity and duration of* gestation among the groups treated with either analogue

RESULTS

Shivering

Table III summarizes the observed incidence of visible shivering (rigors) noted in subjects receiving the prostaglandin analogues The E4 subgroup (5 subjects) were the initial patients treated by the uthors with either analogue The first 2 patients ceived 50 μg doses of 15 methyl PGE2 analogue e remaining 3 patients received 25 μg doses All five patients exhibited profound rigors within a few minutes of the prostaglandin injection much to the *surprise of the investigators* since the previous experience of Karim (14) with similar doses had not emphasized this side *effect*

Subsequent patients treated with the same PGE *analogue* received reduced amounts of the compound both in order to have fewer side effects such as shivering and to ascertain the lowest effective dosage The group which rece*ived the lowest dose* (2 μg) had the lowest incidence and mean number of visible rigors (65%) Of these patients given a 10 μg dose the group receiving the entire list of concomitant prophylactic medications (E3b) had a similarly lower (66%) incidence of rigors The remaining patients receiving the 10 μg dose without premedication had similar higher percentages of shivering (77–83%) The vast majority of thes episodes occurred within 15 min after prostaglan injection There was no tendency for the phenom enon of rigor to increase or decrease with su sequent injections Covering patients with bla k reduced the severity of shivering even though th patients oral temperatures remained elevat Removal of blankets usually brought a return o symptoms

No patient who received a PGF analogue w ever observed to exhibit shivering

Subjective temperature sensations (Table IV)

A subjective feeling of coldness accompanied v ible rigors in all patients thus affected and w occasionally mentioned by patients who were n visibly shivering Subjective cold was experien by 93% of all patients receiving PGE analo while 75% were observed to have shivering Th complaint of coldness like that of shivering o curred shortly after the prostaglandin injection a was attenuated by covering the patient with bl kets There appeared to be no correlation betw the extent of oral temperature elevation and the o set or duration of subjective sensations of coldne

Those patients who received the PGF anal had a low incidence of subjective coldness (1 but a significantly higher tendency to mentio sensation of excessive warmth or flushing (40 than the E subgroups (12%)

Fever (Table V)

Periodic elevations of oral temperature above 38 regularly related to injections of PGE analo were evident in the initial patient group tested (E and are depicted in Fig 1 These patients recei

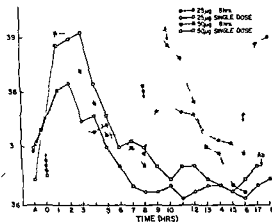
Table III *Incidence of visible shivering (rig among subgroups of patients receiving 15 me PGE2 or PGF2a analogues*

Subgroups	No	%	Mean no episodes	Range
E1	13	65	1 2	0–3
E2	8	80	1 4	0–4
E3a	24	77	1 6	0–5
E3b	30	83	2 1	0–7
E3c	21	66	1 3	0–5
E4	5	100	1 6	1–3
F1	0	0	0	0
F2	0	0	0	0

ɔle IV *Subjective temperature sensations ex ɪenced by patients receiving 15 methyl PGE2 or F2a analogues*

ɪgroup	Feels hot No	%	Feels cold No	%
	2	10	18	90
	0	0	10	100
ı	5	16	27	87
ɔ	[illegible]	5	36	100
:	2	6	29	91
	0	0	5	100
tal E		8		93
	9	45	3	15
	15	38	4	10
tal F		40		[illegible]

or 50 μg doses exhibited maximal fevers at 1–3 ɔurs after each injection All temperatures re ːrted to pretreatment levels in 4–6 hours and re ained there unless subsequent injections were ad ınistered Patients experienced coldness and ıivering while their temperature was rising but did ɔt experience coincident shivers or subjective cold ːelings at times of maximal temperature elevation ı Fig 2 the effect of the same 10 μg dose of 15 ıethyl PGE2 given at 4–8 hour intervals is depicted n all cases there is a prompt temperature rise as ociated with each injection time Injections given t four hour intervals appeared to be too frequent to esult in a return to pretreatment temperatures



ɪg *1* Mean hourly oral temperature in patients receiving tramuscular injections of 15(S) 15 methyl prostaglandin 2 analogue (*A* = admission temperature) Note consistent evation after each injection (↑)

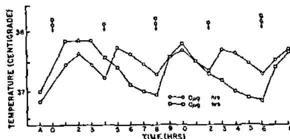


Fig 2 Mean hourly oral temperatures of patients re ceiving 10 μg intramuscular injections of 15(S) 15 methyl prostaglandin E2 analogue at four or eight hour intervals Note consistent elevation after each injection (↓)

while the mean temperature had receded to its basal level in patients injected at eight hour intervals

Patients receiving the PGF analogue (Table V) did not demonstrate any significant overall tem perature elevation although several cases of endometritis (see Table VI) contributed to a slight mean temperature elevation

Effect of concomitant prophylactic medications

The patients in group E3c also received acetylsalicylic acid (aspirin) throughout the induction to-abortion interval Aspirin appeared to exert an anti pyretic effect since this group of patients had the lowest mean hourly temperatures and the smallest percentage of patients (53%) with temperature ex ceeding 38 C at any time during the treatment pe riod This antipyretic effect was best demonstrated in patients of groups E3a b c who received an identical 10 μg dose at four hour intervals (Fig 3) Patients receiving aspirin had a lower mean tem perature although at times the differences were not

Table V *Incidence of oral temperature greater than 38 C among patients receiving 15 methyl PGE2 or PGF2a analogues*

Subgroups	No	%	Fever Maximum	Fever Mean
E1	1	60	38 4	38 1
E2	8	80	39 2	38 4
E3a	26	87	40 2	38 2
E3b	24	67	41 0	38 2
E3c	17	53	38 7	37 8
E4	5	100	39 1	38 3
F1	3	15	38 7	37 4
F2	10	25	38 9	37 6

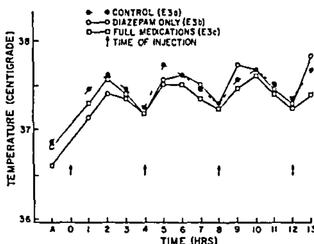


Fig 3 Mean hourly oral temperature of patients receiving 10 μg intramuscular injections of 15(S) 15 methyl prosta glandin E2 analogue at four hour intervals Controls re ceived no additional medications while full medi ations (E3c) group received aspirin prochlorperazine and Lomotil as outlined in Table II

significant Fig 4 shows that the medications exerted no significant effect on the abortion time or cumulative abortion rates in these same three sub-groups of patients (E3a b c) The beneficial effect of prophylactic prochlerperazine and Lomotil for antiemetic and antidiarrheal activity has been re ported elsewhere (10)

Endometritis

e incidence of endometritis was low throughout study except in patients who had cervical la minaria inserted at the time of their initial prosta glandin insertion (group F2) A 10% incidence of endometritis may explain the 25% incidence of febrile episodes noted in these patients

Table VI *Incidence of endometritis in patients receiving 15 methyl PGE2 or PGF2a analogues*

Subgroup	No	%
E1	1	5
E2	0	0
E3	0	0
E3a	0	0
E3b	0	0
E3c	0	0
E4	0	0
F1	1	5
F2	4	10

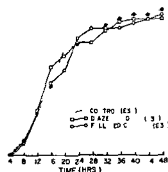
Table VII *Fever associated with E prostaglan*

Reference	Incid ence (%)	Max temp	Dosage
Intravenous PGE2			
Naismith (18)	40	–	0 25–8 0 μg/min
Karim (15)	2	–	5 μg/min
Karim & Filshie (16)	1?	38°C	5–?5 μg/min
Vaginal PGE2			
Henzl (11)	0	–	0 5–? 0 mg (vag s tion)
Jones (13)	70	39 5 C	?0 mg vag supp q
Lauerson (17)	70	40 0°C	?0 mg vag supp q
Freid (9)	100	38 5 C	?0 mg vag supp q
Schulman (20)	33	–	?0 mg vag supp q
Bolognese (3)	55	40 5 C	?0 mg vag supp q 2–4 h
Corson (6)	50	39 7°C	?0 mg vag supp q
Southern (?1)	45	–	?0 mg vag supp q 3–5 h
Extraovular 15 me PGE2			
Choo (5)	4	38 9°C	25 μg single dose
Intra-amniotic PGE2			
Hudson (12)	12	–	10 mg single dose
Intra amniotic 15 me PGE2			
Amy (1)	30	–	100 mg single dose
Intramuscular 15 me PGE2			
Ballard (2)	100		10 mg q 2 h
Karim (14)	12		25–50 mg q 8 h
Gruber (10)	93		10 mg q 4 h
Brenner (4)	65		5 mg q 4 h

DISCUSSION

Although the subject of temperature elevation d to non infectious side effects of prostaglandins u for abortion has not been addressed specifical the literature of human clinical studies m authors have mentioned widely variant inciden of febrile complications associated with admi tration of E prostaglandins

Table VII is a summary listing of several art which mentioned the percentage of patients hav fever in studies utilizing E prostaglandins and th analogues for abortion or term labor induction T disparity of cited observations is striking among studies with identical or nearly iden dosages and routes of administration Presumab most investigators have learned that febrile sodes associated with exogenously administered prostaglandins are transient and without morbid



Cumulative abortion rates of patients receiving intramuscular injections of 15(S) 15 methyl prosta n E2 analogue at four hour intervals The groups ed different schedules of prophylactic medications lined in Table II

e it may be possible that such febrile epi s were ignored or otherwise under reported rwise it is difficult to explain two- or three differences in cited incidences of fever using ame dosages and types of prostaglandins One however be cautious in dismissing fever in cases since morbid fevers of endometritis other infectious origins may be temporarily ted thus delaying appropriate treatment

though the maximum oral temperature re ed by the authors cited in Table VII was 40 5 C eratures as high as 42 5 C have been reported reliminary studies utilizing high dosages of) 15 methyl PGEa analogue Such fever if sus ed might prove injurious Fortunately effec dose schedules now require only a fraction of lose which precipitated fevers of the degree just ribed

he precise pathophysiologic events which lead ever production after E prostaglandin use have been elucidated The initial observation that pyretics are often also inhibitors of prosta idin synthesis was an early clue to the associa Animal studies (8) in which prostaglandins of E type when administered into the lateral ven les or hypothalamus provoked a febrile re nse gave support to a hypothesis that tempera changes were of central origin perhaps in ving an upward displacement of the threshold central thermo-sensitivity (22) Whether or not is a direct prostaglandin effect or is mediated increased production of catecholamines remains culative It is more certain that pyrogen induced er is associated with production of prosta glandins centrally since cerebrospinal prosta glandin levels rise during endotoxin fever (7)

It is also possible that some of the thermal side effects especially the visible shivering and subjec tive feeling of coldness may have both central and peripheral components in so far as the action of prostaglandin is concerned Consistently our own observations revealed that the initial symptom seen usually within minutes after injection of the 15 methyl PGE2 analogue was that of a cold sensation followed shortly by visible shivering These symp toms appeared to be related to surface heat loss since they could be prevented or significantly am eliorated by covering the patients with blankets and would re appear upon removal of the warm covering An attractive hypothesis to explain these observations would be that the peripheral vaso-dilating activity of the E prostaglandin promoted surface heat loss from the subjects thus provoking the initial symptomatology Significant temperature elevation on the other hand was never observed until at least 1-2 hours after prostaglandin injection by which time little or no shivering was present It was also interesting to observe that venous blood sampling became progressively more difficult as time progressed after each injection leading to the speculation that a compensatory veno-constriction had evolved promoting heat retention and tempera ture elevation Such an hypothesis may merit future testing

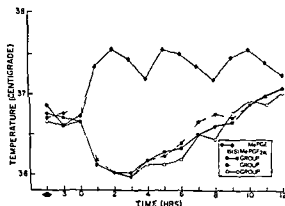


Fig 5 Comparison of mean hourly oral temperatures in patients receiving 15(S) 15 methyl prostaglandin analogues E2 or F2a Patients in Group I and those receiving the E2 analogue had no additional medications Group II patients received prophylactic prochlorperazine and Lomotil (in dosages identical to those of Table II) Group III patients had lamaria inserted in addition to receiving prochlorpera zine and Lomotil No patient in any of the subgroups received aspirin

The E prostaglandins appear to evoke the most consistent and marked temperature elevation in the several animal species studied thus far In contrast F prostaglandins elicit no such rise Our own observations in a previous report (10) illustrated in Fig 5 show an opposite effect i e a transient and significant temperature decline for up to 8 hours after administration of 15(S) 15 methyl PGF2a

CONCLUSION

Administration of E prostaglandins and their analogues by differing routes and dose schedules provoke thermal side effects such as temperature elevation rigors and subjective coldness in a high percentage of subjects In 99 patients having abortion induced with intramuscular 15 methyl PGE2 analogue the concomitant administration of acetyl salicylic acid appeared to reduce the incidence and degree of these side effects The severity of such side effects appears to be dose related) Although the E prostaglandins and their analogues appear to be thermogenic compounds exerting their effects through a centrally mediated mechanism there may also be peripheral vascular actions of these prostaglandins which contribute to the appearance of thermal side effects

ACKNOWLEDGEMENT

Supported by United States Public Health Service Re ch Grant RR46 from the General Clinical Research ters Branch Division of Research Resources and supported in part by a grant from the International Fertility Research Program Research Triangle Park North Carolina (AID/csd 2979)

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Submitted for publication Jan 21 1977

William E Brenner
Department of Obstetrics and Gynecology
The University of North Carolina at Chapel Hill
Old Clinic Building 226 H
Chapel Hill N C 27514
USA

Acta Obstet Gynecol Scand 57 41–44 1978

THERAPEUTIC ABORTION IN AN OUT PATIENT CLINIC

A Prospective Investigation of Complications and Patient Acceptability

Birger R Møller Jørgen Trier Hansen Poul Diederich and Viggo Oram

From the Surgical Out patient Clinic Aarhus Kommunehospital Aarhus Denmark

bstract The incidence of complications associated with ierapeutic termination of pregnancy was analysed in 1349 patients whose average age was ?6 3 years Of the atients 51 8% were 25 years or under 56 3% were seen n or before the 8th week of pregnancy and 17 4% had reviously had one or more legal abortions All the opera ons were performed under local anaesthesia and by the ame doctor who was an experienced gynaecologist omplications associated with the operation occurred in ,4 patients (1%) viz infe tions in the uterus and tubes 9 ases incomplete abortion necessitating repeat curettage cases and profuse bleeding requiring blood transfusion case No uterine perforations or cervical ruptures were ncountered

Questioned about subjective discomforts of the opera on 7 4% of the women answered that the discomfort ad been considerable whereas 6? 6% described it as nly slight 4 8% would have preferred general anaes- iesia

We conclude that therapeutic abortion can be per ormed safely and with an acceptably low incidence of omplications in out patients provided the operations are erformed by an experienced gynaecologist

I'i 1973 a revision of the Danish law concerning regnancy gave all women the right to free abortion fore the end of the 12th week of pregnancy Since ien a steep increase in the number of terminations f pregnancy has occurred (Fig 1)

Up to that time almost all legal abortions were rformed under general anaesthesia during admis on to a hospital However the increasing number f abortions caused great difficulties for the ynaecological departments In our hospital we ave tried to overcome these difficulties by rforming the operations on out patients and un r local anaesthesia This policy might be ex cted to be followed by an increasing number of omplications and therefore a prospective study of such complications was undertaken The experi ence gained during the first 2 years of the period is reported below

MATERIAL AND METHODS

During the two-year period from Jan 1 1974 to Dec 31 1975 a total of 1391 women were referred to our hospital for therapeutic abortion Abortion must be performed be fore the end of the 1?th week of pregnancy reckoned from the first day of the last menstrual period Termination of pregnancy was performed in 1349 of the patients Abor tion was refused on account of the duration of pregnancy in ?1 cases 9 patients were not pregnant 10 changed their minds and 2 had a spontaneous abortion before the opera tion

All the women were referred to the hospital by their general practitioners After history taking each patient was subjected to physical examination a complete blood count and blood grouping In addition Papanicolaou smears and smears for gonorrhoea were routinely pre pared All the operations were performed within 6 days of the examination

All the operations were performed on out patients by the same doctor who was an experienced gynaecologist In all cases the procedure was dilatation by Hegar's method and vacuum aspiration under paracervical blockade In addition the patients received diazepam 10 mg i v

After disinfection of the external genitalia vagina and cervix the cervix was grasped with single toothed tenaculum The local anaesthetic for paracervical block ade (1% lidocaine–0 0005% adrenaline 10+10 ml) was injected in the usual way The operation was started 5 min after the injection

The uterus was sounded and dilated using Hegar's di lators If the uterine cavity was less than 12 cm deep the cervix was dilated to Hegar No 9 If the cavity was deeper the cervix was dilated to Hegar No 11 The corresponding suction cannula was inserted into the uterine cavity By rotating the cannula and drawing it downwards the contents of the uterine cavity were evacuated Afterwards the cavity was explored with a

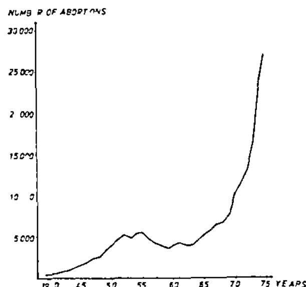


Fig 1 Annual number of legal abortions in Denmark during the last 35 years

small curette All tissue removed was placed in formalin for subsequent histological examination After the operation the patient was given methyl ergonovine maleate (Methergine®) 0 2 mg i m All Rhesus negative patients received anti D immunoglobulin i m This procedure has previously been described in detail by others (7 6 10)

The patient was then moved to a bed in a resting recovery ward where she was observed for 1–2 hours Her vital signs were received during this period and she was checked for bleeding If the patient s condition was satisfactory at the end of this period she left the hospital and was recommended to use no vaginal tampons and no coitus for 4 weeks after the abortion She was also to see her doctor if fever abdominal pain or se bleeding developed The patient was advised to i for a check up examination 1 week later by the tor who had performed the operation The women were examined with special reference to bleeding and infection of the uterus and uterine tubes

Table I *Age distribution of 1391 women applying for abortion*

Age (y)	Patients No	%
Under 16	12	0 9
16–20	225	16 1
21–25	485	34 8
26–30	354	25 4
31–35	169	12 1
36–40	109	7 8
41–45	30	2 2
Over 45	7	0 5
Total	1 391	99 8

Table II *Duration of pregnancy in 1391 applying for abortion*

Duration of pregnancy (weeks)	Patients No	%
Under 9	783	56 3
9–10	40?	28 9
11–12	185	13.3
Over 12	21	1 5
Total	1 391	100 0

At this one week check up examination al were asked whether they found that the surgical dure had given rise to considerable some or only discomfort and whether they would have eral anaesthesia

RESULTS

The age distribution of the 1391 women is shown Table I The average age of the women applying abortion was 26 3 years and 51 8% of them were years or under The duration of pregnancy appe from Table II Of the patients 783 (56 3%) we seen in or before the 8th week of pregnan patients (1 5%) who were in the 13th week or m were refused abortion Table III shows the parity the women applying for termination of pregnan 760 (54 3%) were primigravidae and 49 (3.5%) ha given birth to 4 or more children Of the patie studied 242 (17 4%) had previously had l tion —8 of them (0 6%) on three or more (Table IV) A total of 1271 women (94 2%) turned for check up examination

Among the 1349 patients 14 (i e 10%) some complications associated with the abortion

Table III *Parity in 1391 women applying for tion*

Parity	Patients No	%
0	760	54 3
1	232	16 7
2	249	17 9
3	101	7.3
4	34	2 4
Over 4	15	1 1
Total	1 391	99 7

ɔle IV *Number of previous abortions in 1391 nen applying for abortion*

of previous rtions	Patients No	%
	1 149	82 6
	203	14 6
	31	2 2
	7	0 5
	1	0 1
al	1 391	100 0

A rise of temperature to 38 C or more on 2 suc ssive days after the day of operation or clinical ɲns of endometritis salpingitis and parametritis curred in 9 patients In these cases the infections ɜre treated conservatively with antibiotics and ımobilization Six of these patients were admitted hospital One had profuse bleeding requiring ood transfusion after the abortion The bleeding ıbsided within a few hours and the patient was scharged 2 days later Incomplete abortion neces tating repeat curettage was seen in 4 cases No erine perforations or cervical ruptures were en ɔuntered

On account of the moderate incidence of compli ɪtions we found it irrelevant to correlate them with ɪe age of the patients or the duration of pregnancy

Among the patients 845 (i e 62 6%) experienced nly slight discomfort in association with the opera on while 107 (7 9%) complained of considerable ıscomfort 65 of the patients (4 8%) would have referred general anaesthesia (Table V)

Nearly all the abortions were performed before ıe result of the gono-reaction was obtained and it ıbsequently appeared that 18 women had had a ıerapeutic abortion in presence of untreated ɔnorrhoea No postoperative complications occur ɜd in these patients in particular no signs of ılpingitis developed

DISCUSSION

-veral authors have previously described a variety techniques for the termination of pregnancy in ıe first trimester and have reported widely vary g rates of complications (8 11 13 16) The ıethod used in this study i e vacuum aspiration is well known procedure which has been reported to safe and well suited for out patient intervention (10 14) The complication rates in such studies range from only a few to approx 30% (7 11) In the present study the over all complication rate was low only 1% The most serious complication en countered was a case of profuse bleeding which required blood transfusion Repeat curettage had to be performed in 4 cases A total of 11 patients (i e 0 8%) had to be admitted to hospital after the oper ation

There are probably several reasons for the low complication rate in this study It seems reasonable to assume that wide experience in this particular field may have contributed to this result All the operations were performed by the same doctor who was an experienced specialist in gynaecology and who had performed a large number of termina tions of pregnancy also before the period under consideration

It is well established (5 13) that the incidence of complications of therapeutic abortions is lowest in the 6th to 8th week of pregnancy and that it in creases with increasing gestational age In this study more than half of the patients were subjected to termination of pregnancy prior to the 8th week of pregnancy This is considerably earlier than in other reports (13 16)

All the abortions were performed under local anaesthesia (1% lidocaine adrenaline) Whether this has influenced the degree of complications is unknown but some reports (1 7 9) indicate that the blood loss in relation to operation is smaller when local anaesthesia is used

It is remarkable that 18 patients were infected with Neisseria gonorrhoea in the lower genital tract when the abortion was performed Postoperatively none of these patients showed signs of infections of the uterus or salpinges In acute salpingitis N

Table V *Degree of discomfort experienced by 1349 patients subjected to abortion*

	Patients No	%
Considerable discomfort	107	7 9
Some discomfort	319	23 6
Only slight discomfort	845	62 6
Unknown	78	5 7
Total	1 349	99 8
Would have preferred general anaesthesia	65	4 8

gonorrhoea has been considered the most important causative agent (3 12 15) During recent years other bacteria mycoplasmas (especially M hominis) and chlamydia have been associated with acute salpingitis (4 17) and it now seems that in less than half of the cases N gonorrhoea is re sponsible for infections of the uterus or tubes (17)

We conclude that therapeutic abortions can be performed safely and with an acceptably low inci dence of complications in out patients provided the operations are performed by an experienced gynaecologist In this way the demand for hospital facilities arising from the introduction of free abor tion is greatly reduced The method does not seem to carry with it any great discomfort to the patients

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Submitted for publication Nov 3 1976

Birger R Møller
Miltonsvej 11
DK-8270 Højbjerg
Denmark

Acta Obstet Gynecol Scand 57 45–48 1978

CYCLIC AND STEROID INDUCED CHANGES IN ADRENERGIC NEUROTRANSMITTER LEVEL OF GUINEA PIG UTERUS

G Thorbert P Alm and E Rosengren

From the Departments of Obstetrics and Gynecology Histology and Pharmacology Lund University Lund Sweden

stract The uterine neurotransmitter noradrenaline s examined histochemically and fluorometrically in nea pigs during the estrous cycle and after pretreat nt with sex steroids In diestrous animals noradrenaline ues were higher than in the estrous state Treatment h estradiol or progesterone alone did not markedly luence the level of uterine adrenergic transmitter ereas combined estradiol and progesterone administra n caused a clear-cut reduction in uterine noradrenaline e quantitative changes in transmitter level did not re t the marked alterations in weight during the various erimental conditions and even inverse noradrena weight relationships were observed The findings of further support for the concept of a steroid mediated luence on uterine neurotransmission where the uterine energic nerves constitute a separate target for en rine control distinct from the rest of the uterus

e guinea pig uterus receives a well developed pply of adrenergic nerves which innervate the ometrial smooth musculature as well as the rine vascular bed (20 21) It has recently been monstrated that neuronal noradrenaline in the rus shows marked fluctuations during pregnancy that for example the uterus is almost devoid of radrenaline containing nerves at term (17) Since se dramatic effects on the uterine adrenergic rves can be revealed also in horns lacking fetuses ring unilateral pregnancy (20) it has been con ided that not only mechanical but also humoral tors are involved

t is known that two kinds of adrenergic nerves ich are anatomically and functionally different tribute to the innervation of the uterus (17 19) a basis for understanding the process governing special functional properties of the uterine in vation (16) the anatomy of the adrenergic nerve tem supplying the guinea pig uterus has recently been explored in detail (21) In order to elucidate a hormonal influence on the guinea pig uterine adrenergic nerves changes in the level of neuronal noradrenaline were followed during the normal estrous cycle and after the administration of sex steroids

MATERIALS AND METHODS

Animals The study comprises a total of 31 virgin guinea pigs (body weight 400–600 g) of a mixed strain purchased from a local breeder They were given a standard pellet diet (Astra Ewos Sweden) and water *ad lib* The animals were maintained under constant conditions regarding illu mination temperature and air humidity The estrous cycle was determined by daily inspection of the vagina and when open a smear was taken Before the animals were included in the study at least one estrous cycle of normal length (15–18 days) including two complete estrous phases was observed Animals having pronounced cor nification on a predicted day were considered to be in the estrous phase The day of maximal cornification before the appearance of leucocytes in the smear was designated day 1 of the cycle (7) and diestrous animals were killed on day 9 to day 11 From the diestrous animals a smear was also taken on the day when the animal was sacrificed and only animals with a clear leucocytic dominance were ac cepted for further study

Histochemical and chemical procedures Adrenergic nerves were visualized histochemically using the fluores cence microscopic technique of Falck & Hillarp (3) Nor adrenaline was determined chemically according to the method of Bertler et al (2) as modified by Haggendal (10) The heart and the whole uterus (cervix and the two uterine horns) were used in each determination A minute disc shaped piece was taken from the mid portion of one uterine horn and processed for the Falck Hillarp histo-fluorescence technique (3)

Drugs Progesterone (ACO Sweden) and 17β-estradiol (Draco Sweden) diluted in peanut oil were used Six animals received 0 5 μg 17β-estradiol *sc* daily for 14 days 4 animals received 2 mg progesterone *sc* daily for 7 days

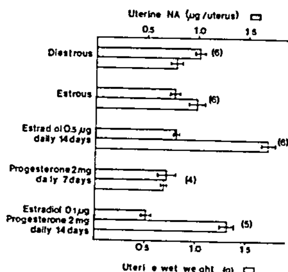


Fig 1 Fluorometric determinations of uterine noradrenaline (NA) and changes in organ weight during estrous cycle and after various sex steroid pretreatments Mean±S E number of determinations (=number of animals) within parenthesis

and finally 9 animals were each given a combination of 0 1 µg 17β-estradiol and 2 mg progesterone administered as two separate daily *sc* injections for 14 days The only criterion for the selection of animals to be subjected to these steroid treatments was that the vagina was closed for three days before the start of the treatment

Statistics Student s *t* test was used in the evaluation of observed differences between mean values

RESULTS

Estrous cycle The uterine adrenergic nerves did not display any clear differences in fluorescence intensity or in number when comparing estrous and diestrous animals However the chemical determinations demonstrated a somewhat higher total uterine noradrenaline content in the diestrous group compared to the estrous group ($p<0\ 05$ Fig 1) On the other hand the difference between the uterine noradrenaline concentrations (µg/g wet weight) was even more marked 1 32±0 11 µg/g (mean±S E) in diestrous and 0 80±0 09 µg/g in estrous animals ($p<0\ 01$)

Hormone treatment Injections with either estradiol or progesterone did not produce any clear cut fluorescence microscopic change Nor did the total content of uterine noradrenaline in the respective groups fluctuate significantly from estrous values ($p>0\ 05$) When comparing these two groups to the group of diestrous animals both estradiol and progesterone treatment were associated with significantly lower amine le ($p<0\ 01$ and $p<0\ 05$ respectively Fig 1)

Combined estradiol and progesterone treatm caused a moderate decrease in intensity of flu cence and the number of fluorescent nerve ter nals This reduction was seemingly more pr nounced in the main part of the uterine horn r less evident in the cervix and the tubal end of t uterine horn This was accompanied by a dis decrease in the total uterine noradrenaline con when comparing either to the diestrous gr ($p<0\ 001$) or the estrous group ($p<0\ 01$)

Uterine weights varied with the endocrine st (Fig 1) In diestrous animals the uterus was sli ly lighter than in estrous animals though the d ference was not statistically significant ($p>0.0$ Both estradiol and combined estradiol/progester treatment caused statistically significant increa weight irrespective of whether the comparison with the estrous or diestrous animals (estr treated animals *versus* estrous or diestrous gr $p<0\ 001$ estradiol and progesterone treated mals *versus* diestrous group $p<0\ 001$ and ve estrous group $p<0\ 05$)

The noradrenaline content and weight of heart innervated by the classical type of symp tic nerves did not fluctuate significantly w comparing the various experimental groups each other ($p>0\ 05$)

DISCUSSION

The guinea pig uterus contains consider amounts of noradrenaline—but no measura dopamine or adrenaline (19)—which is stored in the well-developed system of adrenergic ner within the organ (20 21) These adrenergic ner originate partly from pre and paravertebral gang and partly from paracervical ganglion formati (21) which give rise to the so-called sho adrenergic nerves (17) There is a considerable gional variation in the density of the plexus of ner terminals belonging to short adrenergic neurons well as classical adrenergic nerves both of wh supply the myometrial and vascular smooth cles in the organ In the rabbit the ut adrenergic nerves have a different organiza in that only short adrenergic nerves supply myometrium whereas the classical type inner the vascular bed and no regional variation in

rve supply has been demonstrated The system of ort adrenergic neurons is in many respects func onally different from sympathetic nerves outside e uro-genital tract for example they can be influ ced by treatment with sex steroids which can be vealed in terms of alterations in the amount of the oradrenaline transmitter (17 19)

Substantial fluctuations in the noradrenaline level ... ation to the estrous and diestrous phase could demonstrated in the guinea pig uterus which ggests that the adrenergic nerves are also influ ced by the cyclic hormonal changes occurring ider physiological circumstances This is sup- rted by corresponding cyclic changes in the nor renaline transmitter of human and monkey iducts (8 15) in which the high level during the eal phase agrees well with the values for guinea uterus during diestrous This comparison is rticularly relevant since the guinea pig estrous cle has many similarities to the primate menstrual cle including changes in sex steroids (7 11) It is eresting to note that endogenous fluctuations in rine noradrenaline have also been found during reproductive cycles associated with seasonal riations in the hedgehog (13) It has been claimed some studies on rats that cyclic fluctuations oc r in uterine adrenaline However there is no evi nce that adrenaline has a neuronal localization in uterus and it is therefore conceivable that any clic changes involve extraneuronal stores of this ine (14)

Treatment of guinea pigs with exogenous es gen gave similar values for uterine nor renaline as those measured during the estrous ase although the hormone treatment caused a ore conspicuous increase in the organ weight lministration of progesterone alone caused a less onounced reduction in noradrenaline than did atment in combination with estrogen (9)

The dose of progesterone and estradiol used in combined treatment group was selected from work of Challis et al (5) in order to produce an docrine state with similarities to that of pregnan In the guinea pig (?0) as well as in the rabbit (18) d humans (12) pregnancy causes a prominent rease in uterine noradrenaline That sex steroids y contribute to this decrease is suggested by the luction of noradrenaline seen in the guinea pigs eiving progesterone together with estrogen This a is further supported by the finding of a de ase in uterine noradrenaline transmitter in rabbits during HCG induced pseudopregnancy under conditions when both plasma and uterine pro gesterone are elevated (1 22)

Alterations in uterine noradrenaline in the differ ent experimental groups did not parallel the changes in organ weight Thus opposite effects on weight and noradrenaline were observed during the estrous cycle as well as after the combined estrogen and progesterone treatment a prominent weight gain with no change in noradrenaline was seen after the estrogen stimulation This means that the normal fluctuations in uterine noradrenaline concentration expressed on an organ weight basis are quite con siderable and therefore that the exact cycle stage has to be determined when material from guinea pigs is used as experimental control There is thus further evidence that the uterine adrenergic nerves constitute a target system for steroid hormones separate from the organ proper as reflected by its weight A similar conclusion was drawn from an entirely different experimental model in which the development of the genital tract and its adrenergic innervation was followed after interference of the early differentiation of the hypothalamus by post natal castration or androgenization of male and female rats respectively (4)

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Submitted for publication Feb 27 1977

Gunnar Thorbert
Department of Obstetrics and Gynecology
University Hospital
S 221 85 Lund
Sweden

Acta Obstet Gynecol Scand 57 49–61 1978

URETHRAL PRESSURE PROFILE BEFORE DURING AND AFTER PUBOCOCCYGEAL REPAIR FOR STRESS INCONTINENCE

A Öbrink G Bunne U Ulmsten and
A Ingelman Sundberg

From the Department of Obstetrics and Gynecology Karolinska Institutet Sabbatsberg Hospital Stockholm Sweden

stract In two groups of women the urethral pressure ofile was recorded using a microtransducer catheter th groups were of approximately the same age one isisting of continent women the other of women with ere stress incontinence Sixteen stress incontinent men were examined before and after pubococcygeal air and 10 of these were also examined during the ration The two groups were compared for differences he urethral pressure profile in the continent and incon nt states The stress incontinent women had a signifi itly shorter functional length of the urethra (10 mm) but same maximal urethral pressure as continent women markable changes in these parameters were seen during operation However at the examination 3 months toperatively they had totally disappeared The only inge in the urethral pressure profile which persisted r the operation was a higher pressure in the proximal t of the urethra so that a urethral maximal pressure teau had been established This plateau was also seen a higher level in the continent state

ess incontinence is characterized by urinary kage at a sudden intra abdominal pressure in ase Why a woman becomes continent after a cessful operation is still only partly understood stly it has been supposed to be connected with bladder neck being elevated from its pathologi ly lowered position

The significance of the urethra s length for the intenance of continence has been debated pides (7) reported that an abnormally short thra could explain the existence of stress incon nce This hypothesis was based on measure nts made with a Foley catheter inside the urethra in erect position and the application of the law of place to the urethra

Hodgkinson (4) using the bead chain technique did not find a shorter anatomical length of the urethra in stress incontinent women than in conti nent ones

In 1961 Enhorning (3) showed that neither the anatomical nor the physiological length of the urethra was different in stress incontinent women compared with continent ones (the physiological length according to Enhorning is the distance from the point proximally where the urethral pressure begins to rise above the bladder pressure to the external urethral meatus) The maximal pressure of the urethra was shown to be significantly lower in cases of stress incontinence compared with that in continent women The measurements were performed with simultaneous urethrocystometry using a balloon catheter connected to conventional transducers of variable inductance type The equipment was technically complicated and did not allow continuous recording of the urethral pressure profile simultaneously with the cystometry

A new technique for pressure recordings has been reported (9) It is based on the use of a thin catheter with two microtransducers inside (Millar Instrument Inc Houston USA) connected to conventional amplifiers and to a recorder This method of pressure recording has good precision and reproducibility (1 2) Hence it was chosen for this investigation

The main purpose of the investigation was to study whether any specific changes in pressures in the urethra and bladder were correlated to the transformation from incontinence to continence at surgical treatment Therefore the functional length of the urethra the maximal urethral pressure the

bladder pressure and the urethral closure pressure in stress incontinent women were compared before and after operation Furthermore the urethral pressure profile was recorded at different steps of the pubococcygeal repair operation This we did in order to get a focused picture of the changes in the parameters when the patient became continent A comparison was also made between a control group of continent women and the stress incontinent women pre and postoperatively

MATERIAL

A group of 16 stress incontinent women and a control group of 14 continent women were examined

The stress incontinent group

Sixteen women with a mean age of 57 years (r=77–31) and a mean parity of 2 3 (r=4–0) with genuine stress incontinence were examined All patients suffered from at least stress incontinence of degree II on a scale of three (6) (I) urinary leakage only at coughing or sneezing (II) urinary leakage also at moderate strain (e g walking quickly) (III) urinary leakage even at minimal strain (e g changing position)

None of the patients had previously been operated on either abdominally or vaginally on any gynecological indication Preoperatively the patients had been subject to a uro-gynecological examination including a neurological status of the dermatomes S1 S4 urethrocystoscopy cystometry (Lewis) and sphincterometry (Leander) In all patients a downward rotation of the anterior vaginal wall was seen at coughing

Leakage was present at coughing at a bladder volume of 200 ml and Bonney s test was positive Urinary cultures ~re negative All patients had practiced holding urine ly for at least half a year and had preoperatively been with estrogens (Promarit® Progynon® p o or ® 10–20 mg i m) Ten women in this group chosen at random were also examined *during the operation* All 16 women were examined 3 months after the pubococcygeal repair operation

The control group

Fourteen volunteering continent women with a mean age of 54 years (r=64–48) and a mean parity of 1 2 (r=3–1) were examined None of the patients suffered from incontinence or other disorders of the urinary tract Urinary cultures were negative and the gynecological findings were normal All women were informed of the aim of the investigation and gave their verbal consent to participation

METHOD

Simultaneous urethrocystometry with the urethral pressure profile was performed (9) The recording equipment consisted of a semiflexible dacron catheter with two microtransducers enclosed (outer diameter 2 31 mm) three amplifiers and an ink jet recorder (Siemens Elema Stockholm Sweden) The pressure sensitive areas (diameter 0 75 mm²) were situated one at the tip of the other 60 mm proximally These areas were conne to the microtransducers in the catheter accordin strain gauge principle This pressure recording techni has been described (1 ?) and found to have good precisi and reproducibility With this equipment the bladder pr sure the urethral pressure and the closure pressure we determined simultaneously To record the urethral sure profile and thereby the functional length of ra we used a synchronous motor with an arm catheter could be attached and withdrawn from t der with a velocity of 2 5 mm/s

In both groups of patients three urethral pressur files at rest were recorded at every 100 ml b from 100 ml until the maximal bladder capacity reached Simultaneously the bladder pressure was corded The holding urine profiles bladder volume of 200 ml The stress incontinen were examined preoperatively and three months p operatively

During the operation the urethral pressure profi was recorded after every step of the operation at stant bladder volume of 300 ml 0 9% saline solu (checked three times during the operation) Seven pat among those examined preoperatively were also exam two weeks after surgery This was done with a blad volume of 300 ml or 200 ml if the patient reported tenesmi at this bladder volume

Operation method ad modum Ingelman Sundberg

The steps during pubococcygeal repair are

I Anaesthesia (epidural in all cases except one)

II An arcuate incision is made below the ext urethral meatus The anterior vaginal wall is d sec from the urethra and from the bladder floor up to t cervix

III The bladder ligaments are dissected and sutured the midline from the proximal urethra to the cervix w the innermost suture is fixed Continen e is 300 ml in the bladder at repeated coughs still incontinent at this stage some more fi are added until the bladder neck region is s elevated and the patient continent

IV The pubococcygeal muscles are dissected and tally divided just below the middle

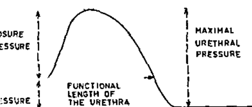
V The anterior portions of the pubococcygeal mus are sutured under the proximal part of the urethra and bladder neck thus creating a muscle sling under the b der ligaments

VI The bulbocavernous muscles are sutured in midline without division as a support for the distal the urethra The operation is finished by a posterior portions of the pubococcygeal muscles ischiocavernous muscles bilaterally The anterior wall is sutured at the introitus a suprapubic applied as well as a vaginal tamponade

Definitions and interpretations

Definitions according to the ICS Standard Comm 1975 (5)

Urethral pressure The pressure within the urethr corded in relation to the atmospheric pressure



1 The curved line represents the recorded pressure m the bladder along the urethra to the external meatus

esical pressure The pressure within the bladder corded in relation to the atmospheric pressure

hral pressure profile Continuous recording of the raluminal pressure throughout the entire length of the thra

Urethral closure pressure The intraurethral pressure nus the bladder pressure

The functional length of the urethra The part of the thra where the intraluminal pressure exceeds the blad pressure

How the parameters are measured from the records is own in figure 1 above

Three urethral pressure profiles were measured at every) ml bladder volume but only the third one was counted the statistical analysis The reason for this was that ne women had more sensitive urethras than others oluntary movements and contractions of the pelvic or might distort the urethral pressure profile Repeated ordings of 10 consecutive profiles under equal condi ns showed that the profiles were almost identical from third one onwards

RESULTS

control group

e mean functional length of the urethra de ased from 32 (r=44–22 5) to 29 (r=42–20) mm en the bladder volume was increased from 100 to 400 ml (p<0 01) The mean physiological gth at 200 ml bladder volume was 37 mm The an distance between the end of the pressure teau and the external urethral meatus was 15

The mean maximal urethral pressure did not nge with increasing bladder volume The mean ues were approximately 38 mmHg The urethral ssure was maximal along approximately 15 mm he profile In that part of the urethra where the ssure was highest there were pressure varia is synchronous to the patient s breath and pulse se amplitudes were 5–10 and 2–5 mmHg re ctively As the pressure sensor area of the catheter moved along the urethra during measurement of the pressure profile these amplitudes diminished

The mean bladder pressure increased from 8 5 mmHg (r=13–5) to 11 mmHg (r=15–7) (p<0 01) A slow continuous pressure increase was seen in all patients

The differences in the parameters at 100 and 400 ml bladder volume were analyzed with Student s *t* test

Light tenesmi occurred at a mean bladder volume of 350 ml (r=550–200) Severe tenesmi occurred at a mean bladder volume of 600 ml (r=800–400) The mean total bladder capacity was 600 ml (r=800–550) The mean urinary residual volume was 4 ml (r=20–0)

The urethral pressure profile at holding urine was recorded in all patients Only five patients could hold urine without a simultaneous contrac tion of the abdominal muscles Changes in both the functional length and the maximal pressure of the urethra were seen when the profiles of these pa tients at rest and at holding urine were compared at the same bladder volume

The stress incontinent group preoperatively

The mean functional length decreased from 23 5 (r=33–17) to 19 5 (r=28–13) mm when bladder vol ume was increased from 100 to 400 ml (p<0 01) The mean physiological length at 200 ml bladder volume was 27 5 mm The mean distance between the maximal pressure point and the external urethral meatus was 12 mm

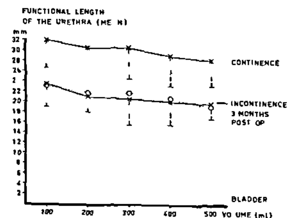


Fig 2 The change in the functional length of the urethra at increasing bladder filling in continent and incontinent women

The mean maximal urethral pressure did not change with increasing bladder volume The mean values were approximately 38 mmHg The urethral pressure profile had a pointed appearance with a distinct maximal point At the point in the urethra where the pressure was highest there were pressure variations synchronous to the patient s breath and pulse Their amplitudes were 5–10 and 2–5 mmHg respectively

The mean bladder pressure increased from 12 4 (r=21–7) to 14 (r=24–9) mmHg (p<0 01) A slow continuous pressure increase was seen in all patients

The differences in the parameters at 100 and 400 ml bladder volume were analyzed with Student s t test

The mean values at 300 ml bladder volume for the 10 patients who were also recorded during the operation were

F=21 5 mm (r=29–13) U=41 mmHg (r=60–28) B=14 mmHg (r=33–8)

F = mean functional length of the urethra
U = mean maximal urethral pressure
B = mean bladder pressure

Light tenesmi occurred at a mean bladder volume of 225 ml (r=300–100) Severe tenesmi occurred at a mean bladder volume of 400 ml (r=500–300) mean total bladder capacity was 450 ml (r=500–300) The mean urinary residual volume was 7 ml (r=20–0)

The urethral pressure profile at holding urine was recorded in all patients Only 5 patients could hold urine without a simultaneous contraction of the abdominal muscles Changes in both the functional length and the maximal pressure of the urethra were seen when the profiles of these patients were compared at rest and at holding urine at the same bladder volume

The stress incontinent group during the operation

The mean functional length increased from 19 5 mm (r=23–16 5) after anaesthesia (step I) to 37 5 mm (r=44–29) after the bulbocavernous suture (step VI) Some increase was seen after the dissection but the largest increase occurred after suture of the bladder ligaments and the bulbocavernous muscles

The mean maximal urethral pressure increased from 26 (r=44–13 5) to 31 5 (r=48–12 5) m[illegible] The total increase occurred after the bladder ligaments had been sutured

The mean bladder pressure decreased in spite of a constant bladder volume from 10 (r=17–4 5) to [illegible] (r=10–2 5) mmHg (p<0 01)

The stress incontinent group 2 weeks postoperatively

F=30 mm U=35 5 mmHg B=13 mmHg

Because several patients still had their suprapubic catheters and some of them had urinary infection calculations regarding the urethral pressure values must be made with caution

The stress incontinent group 3 months postoperatively

Fifteen of the 16 stress incontinent women were cured and one improved at the examination [illegible] months postoperatively The bladder neck [illegible] well elevated and no downward rotation of [illegible] anterior vaginal wall was seen at strain in [illegible] tient

The mean functional length [illegible] (r=28 5–16) to 20 5 (r=25 5–10) mm when bladder volume was increased from 100 to 400 ml (p<0 [illegible]

The mean maximal urethral pressure did [illegible] change with increasing bladder volume [illegible] values were approximately 32 mmHg In [illegible] of the urethra where the pressure was h[illegible] were pressure variations synchronous to the [illegible] tient s breath and pulse Their amplitudes were [illegible] and 2–5 mmHg respectively The urethral pressure profile had a broad maximal plateau

The mean bladder pressure increased from [illegible] (r–20–7) to 15 5 (r=26–9) mmHg (p<0 01) A[illegible] continuous pressure increase was seen in all patients

The differences in the parameters at 100 and [illegible] ml bladder volume were analyzed with S[illegible] t test

The mean values at 300 ml bladder volume for [illegible] 10 patients who had also been recorded during [illegible] operation were

F=22 5 mm (r=26 5–18) U=36 5 mmHg (r=45–23) B=15 5 m[illegible] (r=24–8 5)

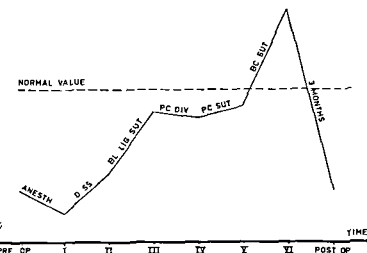


Fig 3 Variations in the mean functional length of the urethra pre per and postoperatively compared to the normal value

ht tenesmi occurred at a mean bladder volume of) ml (r=350–200) Severe tenesmi occurred at mean bladder volume of 480 ml (r=600–350) e mean total bladder capacity was 490 ml 600–400) The mean urinary residual volume s 20 ml (r=90–0)

The urethral pressure profile was recorded in all ients at holding urine Ten out of 16 patients uld hold urine without a simultaneous contrac n of the abdominal muscles Five of these pa nts did show changes in the urethral functional gth and the maximal urethral pressure when 'nparisons were made with the profiles at rest at ' same bladder volume

The urethral pressure profile at rest and at holding urine

		At rest	At holding urine	
Functional length of the urethra (mm)	Preop	21 5	27	=5 5
	Postop	22	25	=3
	Normal	28	34	=6
Maximal urethral pressure (mmHg)	Preop	41 5	50	=8 5
	Postop	27 5	37	=9 5
	Normal	47	56 5	=9 5

All measurements were made at a bladder volume of 200 ml After the operation contraction of the muscle sling brings the urethra chiefly anteriorly without any lengthening

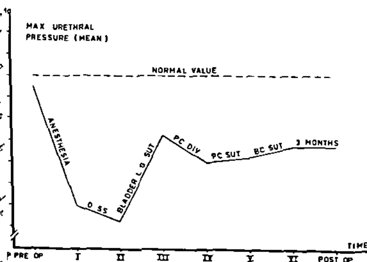
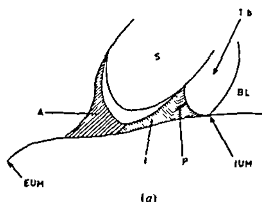


Fig 4 Variations in the mean maximal urethral pressure pre per and postoperatively compared to the normal value



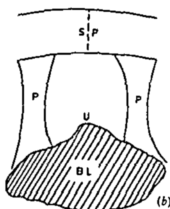


Fig 5 Schematic drawing of the urethral suspension (*a*) Sagittal view (*b*) As indicated by the arrow in *a* *A*=anterior pubourethral ligament *BL*=bladder *EUM*=external urethral meatus *IUM*=internal urethral m *I*=intermediate pubourethral ligament *P* po pubourethral ligament *SP*=symphysis pubis *U* ur

DISCUSSION

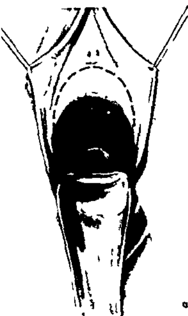
Stress incontinence versus continence

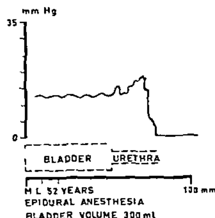
The prominent features of the parameters recorded preoperatively in the stress incontinent group were that the functional length of the urethra was nearly 10 mm shorter in the incontinent patients compared with the continent (see Fig 2) The urethral maximal pressure did not differ between the two groups

The shortening of the functional length mainly affected the proximal part of the urethra Is the short urethral functional length a consequence of the lost ability of some part of the urethra to main n a closure pressure or does it have to do with a of the true anatomical length or is it ,be a combination of the two? According to Hodgkinson (4) the anatomical length is the same in incontinent and continent conditions If this is true the short functional length at incontinence depends on a loss of tone in the proximal part of the urethra secondary to the lowering when the fixation to the symphysis has deteriorated This reduced tissue resistance renders the pressure in the proximal part (7 mm) of the urethra equal to the bladder pressure and this part of the urethra must consequently be filled with urine Possibly this loss of tone gives a more or less prominent funnelling of the proximal urethra as has been shown in radiographic studies (8) However the bead chain technique used by Hodgkinson had a methodical error of ±5 mm The possibility of a minor shortening of the anatomical length caused by the lost symphyseal fixation is therefore not excluded but on the contrary highly probable The urethra is closely attached to the anterior vaginal wall so that when both structures lose their fixation they are not only ered but also shortened Thus it seems tha short functional urethral length the loss of tone funnelling and perhaps a shortened anato length are consequences of the same cause i.e lowered position of the upper urethra Normall bladder ligaments act as a hammock supporting bladder neck Furthermore, the proximal ure held in position and stretched by the fairly st elastic posterior pubo-urethral ligaments contai collagen and elastic connective tissue (Fig When the bladder ligaments lose their attachm to each other and glide apart the bladder neck its support from beneath and the strain on pubo-urethral ligaments becomes too great Co quently the urethra is only fixed to the symph by the anterior pubo-urethral ligament and by of the intermediate ligaments which possibly relax gradually Thus the whole anterior va wall rotates downwards at straining This that all parts of the urethra can be shortened the weight of the full bladder

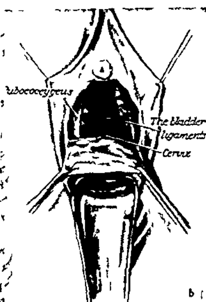
This theory is supported by the fact that the tional urethral length in stress incontinence is formly shortened at increasing bladder volume the control group the numerical shortening of functional length was the same (Fig 7) but in only the upper part of the urethra down to

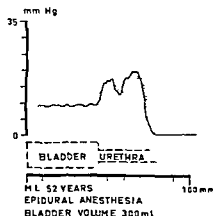
Fig 6 a–f Step wise illustrations of the operat and the corresponding urethral pressure prof in a incontinent woman



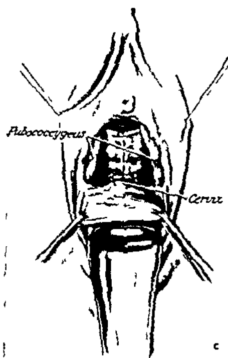


Step I Epidural anaesthesia reduced both the maximal ethral pressure and the bladder pressure by approxi ately 1/3 (41– 6 mmHg and 14–10 mmHg respectively) ne functional urethral length was unaffected In all oper ions the dermatomes Th9 S4 were anaesthetized Thus e sympathetic and the parasympathetic nerves to the smooth muscles were blocked The motor fibers to the striated muscles of the pelvic floor were at least partly blocked Thus the remaining urethral pressure must be maintained by the smooth muscles themselves and to some degree by the striated muscles not blocked

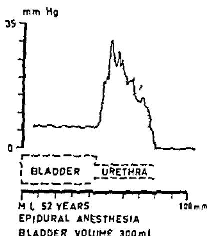




Step II At the detachment of the urethra from the ginal wall the pressure in the proximal urethra increased rkedly in almost all patients In some way the vaginal ll seemed to have a diminishing effect on the pressure in proximal urethra. As long as the urethra was attached the vaginal wall the elastic tissue of the posterior pubo-urethral ligaments could probably not influence the pressure When the urethra was released perhaps these ligaments both elevated the position and increased the tone of the proximal urethra The functional length was unaltered except in three patients where an increase was seen



FUNCTIONAL LENGTH OF THE URETHRA 31m
AREA OF THE FUNCTIONAL URETHRAL PRESSURE PROFILE 706 mm²
URETHRAL CLOSURE PRESSURE 26 mm Hg
BLADDER PRESSURE 6 mm Hg



Step III Repair of the bladder ligaments elevated the bladder floor the bladder neck and the urethra The functional urethral length increased prominently and the maximal urethral pressure slightly These changes were not correlated to each other i e an increase in functional length did not bring about a proportional increase in maximal urethral pressure Possibly these changes were entirely mechanical The bladder ligaments were tightly sutured under the bladder neck and approximately 5 mm of the upper urethra By sheer compression the pressure increased in that part of the urethra which in the incontinent condition physiologically belonged to the bladd When the urethra was elevated the space between the the symphysis diminished Thereby the adipose tissue this space was compressed and exerted a pressure on whole length of the urethral wall Since the urethra can not yield to this pressure not only the maximal press point but the whole urethral pressure profile increas After this phase of the operation there was a solid incr in pressure along the whole urethra the closure press had increased 10 mmHg the bladder neck was in the position and the patients were continent

where the posterior pubo-urethral ligaments are no longer effective (the point on the urethral pressure profile where the pressure starts declining)

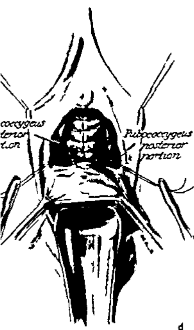
The maximal urethral pressure in the stress incontinent group was as high as in the continent control group and no changes occurred as the bladder was filled However a remarkable difference was that in most cases of stress incontinence the maximal pressure plateau was reduced to a maximal pressure point According to Enhorning stress incontinence is characterized by an abnormally low urethral pressure The discrepancy between his results and ours could be explained partly by the fact that the patients in this investigation had not been operated on before As will be discussed later on an operation of this kind tends to lower the urethral pressure by way of either denervation or scarring or both

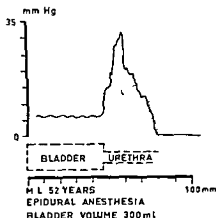
Stress incontinence during surgical treatment

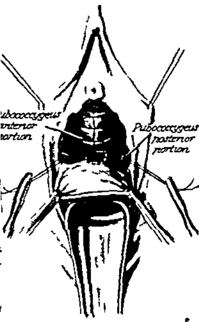
The pubococcygeal repair caused a doubling of urethral *functional length* and a slight incr the maximal urethral pressure The bladder p sure decreased by 1/3 (10–7 mmHg) in spite of constant bladder volume Thereby the marg incontinence (closure pressure) increased A steps in the operation brought about most of changes (Table I and Fig 6a–f)

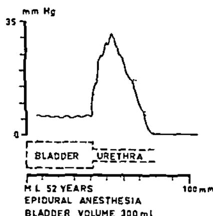
Two weeks after surgical treatment

From the appearance of the urethral pressure p file 2 weeks postoperatively it was obvious that effect of the bulbocavernous muscle suture had appeared in most patients Besides some pati had a more pronounced shortening of the fu length probably caused by a slackening of th tured bladder ligaments

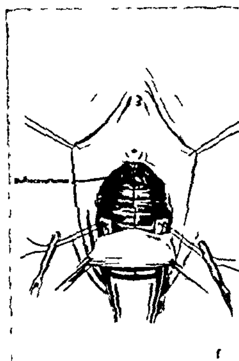


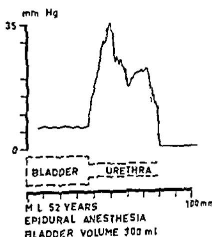






teps IV and V When the pubococcygeal muscles had n divided and sutured no significant changes in the ameters were recorded However the appearance of pressure profile changed markedly so that the profile ame more pointed This implies that the levators were not totally anaesthetized by the epidural anaesthesia Another important conclusion was that the levators con tribute to the urethral pressure at rest although these muscles have been shown to have no muscle fibers in termingled in the urethral wall





Step VI The bulbocavernous suture brought about a sharp rise of the urethral pressure profile distally and thus an increase in the functional length This must be due entirely to the hard compression exerted by the und[illegible] bulbocavernous muscles creating a sling under the [illegible] part of the urethra

The maximal urethral pressure was lower than would have been anticipated from the last recordings during the operation even allowing for the calculated influence of the anaesthesia The reason [illegible] decrease could probably be the diminished [illegible]sing effect of the bladder ligament and the [illegible]ation at the urethral dissection

Three months after surgical treatment

Of the 16 patients 15 were cured and 1 improved The elevated position of the bladder neck and the proximal urethra was maintained in all cases [illegible] functional length of the urethra was reduced to [illegible] same level as before the operation In [illegible] the lengthening effect of the bulbocaver[illegible] muscle suture had almost disappeared or the [illegible]ture was located so far distally that it did no[illegible] ence the urethral functional length In [illegible] this reduction of the functional length there [illegible] decrease probably caused by slacken[illegible] bladder ligaments Thereby the compression [illegible] most proximal part of the urethra was lost and [illegible]

Table I *Summary of the parameters for the woman in Fig 3*

The urethral pressure profile during pubococcygeal repair of stress incontinence

	Functional length (mm)	Functional area (mm²)	Closure pressure	Bladder pressure	Max urethra pres
Anesthesia	21	100	7	12	19
Vaginal wall dissected	28	370	10	9	19
Bladder lig sutured	33	706	26	6	37
Pubococcygeal muscles cut	30	705	24	6	30
Pubococcygeal muscles sutured	32	834	25	6	31
Bulbocavernous muscle sutured	43	1 291	28	6	34

umed its original appearance i e physiologically ad become part of the bladder

From the operative recordings it might have been pected that the high urethral pressure would rsist to some extent after the operation and give increased margin to incontinence However eady 2 weeks after the operation the urethral ssure had been reduced and after 3 months it s further reduced and even lower than in the ontinent condition before the operation The thra was no longer compressed against the mphysis In most patients there was a definite crease in the urethral pressure at the division of pubococcygeal muscles during the operation ich did not always influence the maximal pres e This could partly explain the urethral pressure luction Probably a third contribution to the pres e decrease was denervation brought about at urethral and bladder dissection The importance postoperative urethral scarring cannot be esti ited with certainty after this short observation ie

The pointed appearance of the urethral pressure ofiles before the operation was changed post eratively Now most profiles had a broad pres e plateau similar to those seen in the control oup but of significantly lower magnitude Perhaps s pressure plateau is an advantage for the untenance of continence The pressure plateau licates an increase in the pressure in the proximal rt of the urethra This could be explained by a covery of urethral tone accomplished when the thra is released from the vaginal wall and by er compression from the supporting tissues (the vic fascia and the pubococcygeal muscle sling) g 7)

ordings at holding urine

ssure recordings of holding urine profiles re made in the control group and in the stress ontinent group pre and postoperatively

At contraction the levator muscles compress the thra and elevate the bladder neck via the fascia vis In the control group there were 2 women out 7 whose levator contractions did not cause any inge in the profile Five out of 10 women in the ss incontinent group acted in the same way iong the patients with good levator function the inges in the functional length and the maximal thral pressure were equal in both groups Evidently a good levator function can be compatible with severe stress incontinence None of the stress incontinent women had experienced any improvement after half a year of exercise in holding urine Thus it seems useless to try to improve severe stress incontinence in this way But as it is important to have well trained levator muscles at the operation in order to get a strong muscle sling afterwards exercise in holding urine should be recommended for at least a short period preoperatively After the operation 5 out of 10 women could contract their muscle slings as seen by the ability to influence the profiles The urethral maximal pressure was increased as much as at holding urine preoperatively

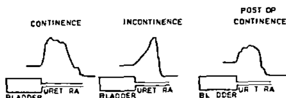


Fig 7 The typical appearance of the urethral pressure profile at the different conditions shown in the figure

The functional length of the urethra was not increased to the same extent as before the operation As the levators had been divided and rearranged they could not exert the same effect on the functional length through the elevation of the bladder neck

Other changes induced by the operation

When dealing with incontinent patients one frequently finds urgency mingled with the stress component Hitherto this has been regarded pretty much as a contraindication for surgical treatment At this investigation a remarkable finding was that the operation seemed to increase the bladder capacity and make the patients feel light and severe tenesmi at higher bladder volumes than before (225–300 ml and 400–475 ml respectively) The reason could be the denervation at the operation and also the fact that the patients did not need to risk urinary leakage when the bladder was full postoperatively Therefore they voided more seldom after the operation and their bladder capacity was normalized Consequently even patients with a minor degree of urgency in their stress incontinence might be totally cured after pubococcygeal repair

A possible risk with several types of operation for

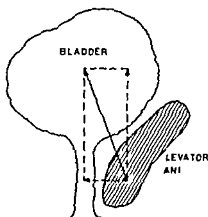


Fig 8 The action of m levator ani on the urethra and the bladder

stress incontinence is to elevate the bladder neck too much with urinary retention as a result Only one patient had a slightly increased residual volume (90 ml) 3 months after the pubococcygeal repair

Theoretical and practical aspects of surgical treatment

Apparently the urethral pressure profile may give valuable information for the choice of operation method If the urethral pressure before the operation is lower than normal it may be hazardous to use pubococcygeal repair or the Zoedler operation because the denervation of the bladder neck and the urethra may cause a further reduction In cases a modified urethrocystopexia operation be the method of choice The dissection be the symphysis and the urethra should then be avoided as much as possible and only the bladder neck fixed to the symphysis

This investigation has shown that the urethral pressure at rest is partly dependent on intact levator muscles Division of these muscles eliminates part of the urethral pressure Possibly this side effect is more than compensated by the supporting and compressing effect of the muscle sling on the proximal urethra at straining

The risk for elongation and prolabation of the cervix is considerable if the bladder ligaments are sutured to the cervix whereby the force on the uterine suspension at straining becomes too great

Suture of the undivided bulbocavernous muscles did not contribute to the results and should be omitted Perhaps a more lasting support under the distal urethra could be obtained if these muscles are divided and arranged as a muscle sling under the distal urethra

The epidural anaesthesia proved to be most suitable for this type of operation Continence could be controlled by asking the patient to cough during the operation Besides the patients were spared coughing and straining at the end of a general anaesthesia which could of course result by rupturing the sutures in the ments and the muscle sling

CONCLUSION

This paper aimed at studying the changes in urethral functional length and pressure before and after pubococcygeal repair and these parameters pre and postoperatively in a continent control group It has been shown that urethral functional length was markedly shorter and the pressure in the proximal part of the urethra lower in the incontinent women compared with continent ones A remarkable finding was that maximal urethral pressure did not differ between the two groups The urethral pressure profile mostly had a quite different appearance with sharply pointed pressure profile in the incontinent women compared with the continent women in whom a pressure plateau was the rule months after the pubococcygeal repair the pressure profile had assumed the pressure plateau appearance seen in the continent control group although on a markedly lower level The functional length of the urethra was the same before and after the operation i e 10 mm shorter than in the control group At the operation the functional length was doubled and the maximal urethral pressure increased Both these changes were probably caused mechanically by dissection and compression increase in the functional length and the maximal pressure did not persist after the operation probably because of denervation scarring and depression as the bladder ligaments slacked slightly

Half of the operated patients were able to contract their pubococcygeal muscle slings and prominently increase the urethral pressure to the same extent as in the continent women

The restoration of the pressure plateau was the only change in the pressure profile which persisted after surgical treatment Perhaps it is secondary

-malized position of the bladder neck and an im ved tone of the proximal urethra which possibly if importance for the maintenance of continence o circumstances have been shown to be of com ed importance for the transformation to conti ice and the continent condition namely the ele ed position of the bladder neck and the good re in the most proximal part of the urethra seen the urethral pressure profile To get further from standpoint in understanding the genesis of uri y stress incontinence it seems essential to luate the changes in the pressure of the urethra the bladder also in a dynamic situation

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Submitted for publication Feb 27 1977

A Öbrink
Department of Obstetrics and Gynecology
Sabbatsberg Hospital
Stockholm
Sweden

Acta Obstet Gynecol Scand 57 63–68 1978

SOME METHODOLOGICAL ASPECTS ON THE MEASUREMENT OF INTRALUMINAL PRESSURES IN THE FEMALE UROGENITAL TRACT IN VIVO

Kjell Lindstrom and Ulf Ulmsten

From the Department of Biomedical Engineering and the Department of Obstetrics and Gynecology University Hospital of Malmo Malmo Sweden

tract This short survey presents some methodological cts on intraluminal pressure recordings *in vivo* from female urogenital tract The importance of adequate oration is stressed and a calibration unit for different s of recording equipments is described Calculations neasuring errors are outlined The selection of record catheters is discussed from both the theoretical and the tical point of view Finally some practical aspects are sidered on pressure recordings *in vivo* from the ureter bladder the urethra and the uterus This discussion is trated by pressure diagrams obtained with different ording techniques from the actual organs

asurement of intraluminal pressure has been ely used for assessing the function of the genital tract However owing to the inaccuracy he methods used the results have often been onsistent and difficult to interpret Rigorous de ids are placed on the measuring equipment cially relating to the properties of the catheters ge stiff catheters can cause damage or artificial ension of the walls of the organ investigated ng erroneous recordings as a result On the r hand the necessity of using relatively long catheters for pressure recordings in the urogen tract implies a risk of defective pressure trans ion in the measuring system especially when ventional open-end fluid filled catheter systems used

ı order to avoid or at least minimize technical suring artefacts the intended equipment must horoughly checked *in vitro* in order to find out ther it has sufficient capacity to record the sure variations in the organs in question This ures a reliable calibration instrument implying possibility of calibrating the measuring equip t *in vitro* and also the possibility of calculating the magnitude of the potential technical errors during *in vivo* measurements Such a calibration unit is described in Fig 1 It offers the possibility of testing practically all types of presently available catheter recording systems

As a general rule of thumb the rise time (~the inertia) of the measuring system should be three times faster than that with which the physiological rises in pressure occur If the physiological

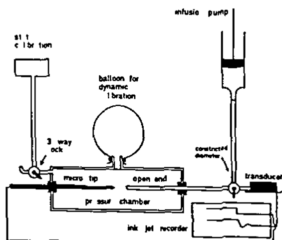


Fig 1 Calibration unit used for static and dynamic calibration of different pressure recording systems The pressure chamber is situated in the middle of the figure At the upper part of the chamber there is a balloon which can be inflated by air thus causing an optional pressure within the pressure chamber In this figure two pressure recording systems are tested (*Left*) a micro-tip-transducer (*right*) an open end catheter connected to a conventional transducer Static calibration can be performed since the pressure chamber is connected to a water column (*upper left*)

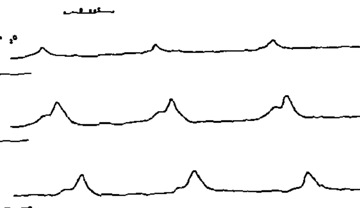


Fig 3 Normal antegrade ureteral peristalsis recorded with a centrum-hole catheter as described in Fig 2. The upper trace reflects the pressure 25 cm from the bladder the middle trace the pressure at 15 cm and the lower trace the pressure 5 cm from the bladder The first rise in pressure as seen most markedly in the middle and the lowermost tracings indicates a bolus of urine The contractions start at upper part of the ureter

What static and dynamic properties should the measuring system possess in order to allow reliable measurements in the organs examined? Does our recording system meet these requirements? Expressed in other words what measuring errors must be expected and within what limits are the measurements valid?

the above questions can be answered with the p of a reliable calibration unit But there is also a rd question to be answered which is most important To what extent is the patient exposed to ks by the intended measurements? This question ist be carefully assessed from an ethical point of w and before any measurements are made the vestigator must inform the patient about the na re of the examination and obtain her consent

nical applications

will close this brief description by demonstrat some pressure diagrams obtained with our different techniques for pressure recordings in the female urogenital tract.

When recording the intraluminal pressure in the ureter it is of great importance that a thin catheter does not obstruct the flow of urine through the organ However the intra-ureteral recording is of *minor value if the* pressure measurements are not performed on at least three intra-ureteral levels Otherwise it is not possible to calculate the direction and rate of propagation of the peristaltic waves The solution of this pressure recording problem is to perform recordings with a central hole catheter (Fig 2) Fig 3 shows an intra ureteral pressure recording with such a catheter in a patient with normal antegrade ureteral peristalsis In Fig 4 retrograde ureteral peristalsis is demonstrated in a pregnant woman admitted to the hospital because of pain in the right flank

Pressure recordings from the lower urinary tract can be very helpful in diagnosing different types of urinary incontinence To obtain a reproducible

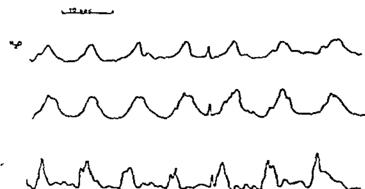


Fig 4 Retrograde peristalsis in a ureter from a pregnant patient. The same recording catheter and recording levels as described in Fig. 3 The ureteral contractions start at the lowermost recording level i.e nearest the bladder At the arrow the patient coughs which indicates that the pressure is transmitted equally from the three recording channels.

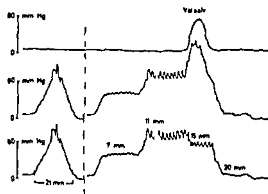


Fig 5 Continuous urethral pressure profile obtained with a micro-transducer catheter The top trace indicates the bladder pressure the middle trace the maximal urethral pressure and the lowermost trace the difference between the urethral pressure and bladder pressure i e the urethral closure pressure At the beginning both the transducers (Fig 6) are situated within the bladder The catheter is then withdrawn from the urethra at a constant rate By this manoeuvre the intra urethral pressure is recorded throughout the entire length of the urethra giving the urethral pressure profile as seen in middle trace left part of the diagram In the right part of the figure the procedure is repeated but the withdrawal is halted at different sites in the urethra It is then seen that when the catheter is halted in the middle part of the urethra at about 11 mm from the inner meatus the highest intraluminal pressure is recorded and at this site marked pulsations synchronous with the patient heart beats are present Finally it can be seen that a Valsalva manoeuvre affects the bladder and urethral pressure equally

urethral pressure profile (Fig 5) and to be ab record the rapid pressure variations in the bl and the urethra caused by coughing or intra abdominal pressure increases (which ca cupy less than 50 msec) it is necessary to u pressure recording system with a high frequ response The microtransducer catheter (Fig 6 fers the best solution for this recording proble must be emphasized that pressure recording lower urinary tract should offer the possibil record the bladder pressure and the maximal urethral pressure simultaneously—otherwise difficult to evaluate functional disorders in tract Fig 7 demonstrates normal micturition young healthy female As seen there is at the tion of micturition a rapid fall in the intra ure pressure and later on there is an increase in intravesical pressure indicating activation detrusor By electronic subtraction of the bl pressure from the maximal intra urethral press is possible to obtain the urethral closure pressur positive closure pressure indicates whereas a closure pressure of zero or below indicates incontinence as seen in Fig 8

The uterine muscle contracts slowly and for tively prolonged periods This means that no demands on the frequency response of ing system is necessary However as rel

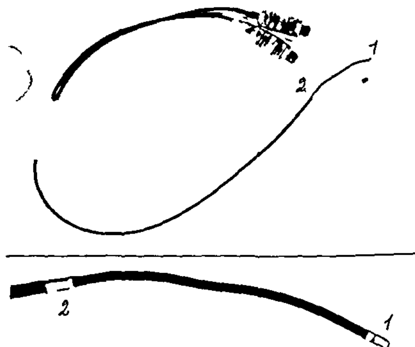
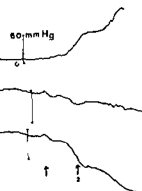


Fig 6 Micro-transducer The pressures are recorded two micro-transducers hos are enclosed in a Dacron ca he cm apart The is only 0 75 mm² At the botto the figure the catheter is shown about four times enlarged



7 Initiation of micturition in a healthy female (micro sducer catheter) *Bp*=bladder pressure *Up*= hral pressure *Clp*=urethral closure pressure At rrow 1 the patient is requested to micturate and there marked fall in the urethral pressure and the closure sure At the arrow 2 the closure pressure reaches zero urine begins to escape from the urethra

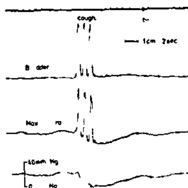


Fig 8 Pressure recordings from a patient suffering from stress incontinence Micro-transducer catheter same recording technique as illustrated in Fig 7 When the patient coughs the closure pressure falls to zero and a small amount of urine escapes from the urethra

ed recordings are necessary to characterize ometrial activity this aspect places high demands the function of the recording equipment We found that the micro transducer technique as d at present seems to be the best method for onged intra uterine recording in the non gnant uterus (10)

o far most pressure recordings from the non nant uterus have been performed during sta conditions but a recently introduced technique ns to offer possibilities to perform dynamic lies of the intact human myometrium (5)

n the *pregnant uterus* great interest has been ussed on myometrial activity during labor and nsive work has been done on this subject in this ntry (3 4 6 7) It is not possible to quantify metrial activity by means of external toc etry Intra uterine pressure recordings via scervically introduced recording catheters in e the risk of rupturing the membranes and fore cannot be used if it is not intended to er the patient in conjunction with making the rdings We have to admit that recording intra ine pressure of the pregnant uterus is difficult as yet no ideal method exists (8) There is siderable need for more accurate non invasive hods In the development of such methods the t accurate present available technique for ulating myometrial activity during labour must sed as reference In our opinion this implies the of simultaneous ultrasound measurement and intra uterine pressure recordings with the micro-transducer technique (8) From such an arrangement the tension of the uterine muscle can be calculated with a relatively high degree of accuracy

Combined pressure recording and ultrasound measurement can also be used to calculate the effect of uterine contractions on the cervix (8)

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Submitted for publication Feb 27 1977

U Ulmsten
Dept of Obstetrics & Gynaecology
Allmänna Sjukhuset
S-214 01 Malmö
Sweden

Acta Obstet Gynecol Scand 57 69–71 1978

FOLLOW UP STUDIES IN DYSPLASIA AND CANCER IN SITU OF THE CERVIX UTERI

Vlasta Vaclavinkova Anna Kristina Hedman and Karen Nasiell

From the Department of Obstetrics and Gynecology Karolinska Institutet Stockholm Sweden

tract In order to study when recurrences appear fol ing conization for dysplasia or cancer in situ of the ix uteri a series of 477 patients has been investigated y all underwent conization at Sabbatsberg 1965–1970 ong the 181 cases of dysplasia two developed recur es one respectively three years after treatment In the s of 296 patients with cancer in situ thirteen recur es appeared Eight of them were detected within the three years The other five were spread out during the four years About 50% of all patients had been wed up for five years or more (Table I) The conclu is reached that a yearly follow-up is necessary for at t ten years As it is impossible to take care of such an imulating number of examinations at the Swedish de ments of obstetrics and gynecology without extra onnel the following proposal is made During the first e years after treatment the examinations are per ed at the department where the conization has been ormed After that period the follow up is limited aginal smears taken once every year in connection the general gynecologic health control

owing preliminary studies (3 4) systematic ecologic screening started in Sweden 1966 Vag smears were taken by midwives to begin with in women in age groups at maximal risk and on successively including both older and nger women The aim was that a smear should aken in every woman every fourth year In spite e fact that only one third of the counties took in the campaign in the beginning the number corded cases of cancer in situ was doubled dur he first two years The result has been a steadi icreasing number of patients in whom regular w up examinations are needed after conization ing a heavy burden for the different depart ts of obstetrics and gynecology The routine at ent seems to be that the patients are examined ast once every year A study has therefore been made in order to investigate if the interval between the follow up examinations could be extended after a certain number of years

MATERIAL

181 cases of dysplasia of the cervix and 296 patients with cancer in situ treated by conization between 1965 and 1970 at the Sabbatsberg department of obstetrics and gyne cology have been studied They have regularly been followed-up with colposcopy and smears at a special weekly clinic by a doctor trained in colposcopy Unfor tunately however several of them have been lost during the time of observation Thus all have been followed up for at least one year but only about 50% for five years or more The age distribution in the group is shown in Fig 1

METHODS

When the diagnosis of dysplasia or cancer in situ had been obtained on biopsies usually directed with the help of the colposcope a conization was made The aim was to make a longer cone in postmenopausal women than in those of fertile age and to perform a curettage of the rest of the cervical canal As however the operation was performed by several different young colleagues the technique and accuracy may have varied

The pathologic examination was made at the Sabbats-berg Institute of Pathology on eight evenly distributed tissue slices cut radially around the cervical canal through the whole length of the cone Histologically radical exstir pation of the lesion was obtained in 90 1% of the cases of dysplasia and in 81 1% of those with cancer in situ If the smear was completely negative one month after the opera tion no repeat conization was performed even if the cone had been incomplete Otherwise repeat conization was undertaken

Those cases were classified as recurrences where atypia appeared histologically after at least one year of negative colposcopy and smears

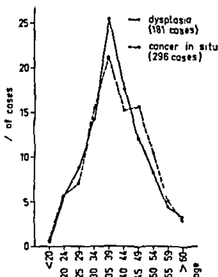


Fig 1 Age distribution

RESULTS

Among the 181 cases of dysplasia recurrences ap peared only in two cases (Table I) one and three years after the conization respectively In both cases dysplasia was present in the margin of resec tion The recurrence was classified as cancer in situ in both cases

Among the 296 cases of cancer in situ thirteen patients had recurrences two as late as six and seven years after the conization (Table I) In three them the cones had been judged histologically as lete and in ten cases cellular atypia was pres in the margin of resection All had their primary cancer in situ at the squamo-columnar junction In nine patients the recurrences were classified as dysplasia and in four as carcinoma in situ No case of invasive carcinoma was diagnosed

In two patients carcinoma of the endometrium was diagnosed four and eight years respectively after the conization and one was operated on for an ovarian carcinoma ten years after the primary oper ation

DISCUSSION

An adequately performed radical conization is an excellent treatment for dysplasia as well as for cancer in situ of the cervix but is no guarantee of cure as three of our recurrences appeared in such cases However several authors state (1 2 5 6) that they have never observed a recurrence a radical conization whereas Zippel (7) had obser recurrences as late as fourteen years af conization The latter observation seems to be l cal as a conization can never remove local disposing factors for the development of ca *The appearance of other types of genital* can e three women of this series during the time of ob vation may also indicate a general disposition cancer among women with dysplasia or cance situ of the cervix A careful follow up is theref necessary

CONCLUSIONS

In our series the recurrences are spread out o more than seven years as seen from Table I N of them however appear within the first th years after the conization

As it is important to diagnose a recurre *early as possible follow up* examinations ea year seem to be necessary for a period of at le ten years

The accumulation of new cases every year m it however impossible for the present staff at Swedish departments of obstetrics and gynecol to carry out all these examinations It is the p proposed that the follow up during the first th years takes place at the department where the c ization has been made After that period the ex nations should be limited to vaginal smears ta once every year by midwives who *operate* m gynecologic screening tests

Table I *Recurrence frequency during t observation*

Follow up after years	Dysplasia No of cases	Recur rences	%	Cancer in situ No of cases	Recur rences
1	181	1	0 6	296	2
2	169	0	0	284	5
3	151	1	0 7	250	1
4	136	0	0	211	1
5	96	0	0	170	2
6	62	0	0	171	1
7	40	0	0	86	1
8	28	0	0	64	0
9	19	0	0	30	0
10	14	0	0	12	0
11	1	0	0	2	0

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Submitted for publication Nov 18 1976

Vlasta Václavínková
Department of Obstetrics and Gynecology
Sabbatsberg Hospital
113 82 Stockholm
Sweden

Acta Obstet Gynecol Scand 57 73–78 1978

PREMALIGNANT AND MALIGNANT UTERINE CHANGES IN IMMUNOSUPPRESSED RENAL TRANSPLANT RECIPIENTS

Hugo Husslein Gerhard Breitenecker and Gerhart Tatra

From the 2nd Department of Obstetrics and Gynecology University of Vienna Medical School Vienna Austria

tract 29 female immunosuppressed renal transplant pients were examined gynecologically In 2 cases the helium of the portio was found to be dysplastic while ometrial carcinoma was present in 1 patient A review ie literature suggests that immunosuppressed patients more likely to develop tumors than others The au s stress the need for gynecological and cytological minations at short intervals to identify premalignant early malignant uterine changes at a time at which e can readily be treated without discontinuation of the iunosuppressive therapy

iough the techniques for tissue typing have be ie increasingly sophisticated recipients of organ isplants still have to undergo prolonged un cific immunosuppressive therapy to reduce the cts of host transplant incompatibilities and as a ilt increase the chances for successful organ isplantation Immunosuppression is currently uned with ionizing radiation cytostatics (al iting agents antimetabolites antibiotics etc) icosteroids and antilymphocyte sera

owever the resultant interference with the or sm s immune responses is associated with un rable side effects including primarily an in ised susceptibility to infections

bservations made in the past few years ap to suggest an accumulated incidence of gnancies (de novo tumor growth) in im iosuppressed renal transplant recipients who in account for the major share of all transplant nts The genital region has been found to be of the areas affected This prompted us to iw up our own material of female immuno- pressed renal transplant recipients gynecol ally

MATERIAL AND METHOD

In the past 12 months 29 female renal transplant recipients underwent gynecological examinations The patients age ranged from 13 to 50 years (mean age 33 years) Kidney transplantation had been performed 2 to 100 months (mean 22.5 months) ago All patients have received post transplantation immunosuppressive therapy Current medication consists of antimetabolites in 26 cases alkylat ing agents in 4 cases and corticosteroids in 27 cases

Follow up studies included gynecological examination colposcopy microbiological investigation of Gram stained smears and cytology of cervical smears Histolog ical studies were done in 3 cases In 2 with positive cytol ogy on cone biopsies processed by serial step sections and in 1 on curetted material and after extirpation on the entire uterus

RESULTS

(a) Clinical gynecology and colposcopy

On palpation 22 females were normal while the uterus in the remaining cases was found to be appreciably smaller than normal The lower pole of the transplant kidney was consistently palpated in a left or right parauterine location There was no evi dence of adnexal pathology or parametrial infiltra tion In 1 case extensive recurrent vulvar vaginal and perianal condylomata acuminata was present

Colposcopy of the portio brought to light a great many abnormalities Coalescent to disseminated iodine negative areas of variable extension in an otherwise normal epithelium constituted the most common finding such areas being present in 14 cases Ectopia was found in 6 females a transfor mation zone in 5 Four patients showed true ero sion while 6 had additional slight leukoplakia Normal portio epithelium was only seen in 4 cases

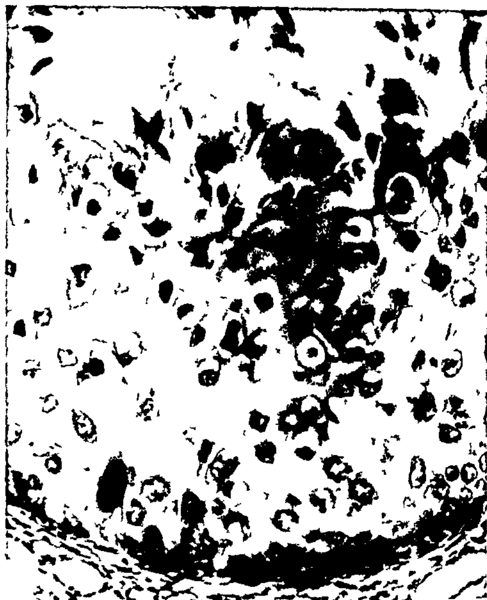


Fig 1 Dysplastic squamous epithelium at the uterine cervix 24 months after kidney transplantation H & E ×100

(b) Microbiology

In 2 cases gram stained smears were clear of microorganisms on microscopy Mixed bacteria were present in 20 cases fungi in 15 Trichomonas associated with candida albicans were found in one female

(c) Cytology and histology—case reports

Cervical smears were negative cytologically in 27 cases Three females showed premalignant or malignant uterine changes

Case 1

This 32 year-old female had received a kidney [illegible] 24 months previously The smear showed [illegible] karyotic squamous cells Conisation was [illegible] histological evaluation The distal cervical canal [illegible] areas of atypically proliferating squamous epithelium [illegible] abundant cellular atypia highly polymorphous [illegible] nuclei and abnormal mitoses extending into the [illegible] epithelial layers The stratification of the epithelium [illegible] still maintained the epithelial cells were rich [illegible] plasm This dysplastic epithelium was also found [illegible] cal glands the epithelio-stromal junction was [illegible] served (Fig 1) Excision of this atypical epithelium [illegible] tended well into intact tissue Still atypical cells [illegible]



2 Normal endometrium in material obtained by ettage from a 44 year-old patient 8 months after kidney nsplantation H & E ×59

un visible on cytology 6 weeks after conization Col copy of the portio showed leukoplakia with an iodine zative area The patient is followed up cytologically and poscopically at short intervals

re 2

is 30-year-old female received a transplant kidney at other hospital 8 years ago Thirty six months prior to uization somewhat atypical cells were first found on ology From then on smears were taken at intervals of nonths Since atypical cells were found to be more indant conization was done On histology dysplastic thelial areas were seen around the last cervical gland as l as in the squamous epithelium on the ectocervix ending down to the vaginal resection line Cytologic ow up studies again revealed atypical cells On col copy extensive iodine negative areas extending into fornix and a slight leukoplakia of the portio were seen low ups are continued at short intervals

e 3

s 44 year-old female underwent renal transplantation 8 nths before curetting was performed for metrorrhagia The histological examination of the curetted material re vealed endometrial tissue with loss of function There was however no evidence of malignancy (Fig 2) Twelve months later i e 20 months after transplantation a polypoid structure protruding from the cervical canal was removed and the curettage repeated The endometrial tis sue obtained showed areas of highly differentiated adenocarcinoma These prompted total extirpation of the uterus Both the endometrium and the mucosa along the isthmus of the uterus were largely replaced by highly differentiated adenocarcinomatous tissue infiltrating the innermost myometrial layers (Fig 3)

DISCUSSION

Ionizing radiation antiproliferative substances (cytostatics) corticosteroids and antilymphozyte sera can be used to suppress immune responses to transplants Generally the suppressive agents available are used in combinations However the resultant interference with the organism s immune



Fig 3 Same patient as in Fig 2 12 months later highly differentiated endometrial adenocarcinoma H & E ×59

mechanisms causes a number of undesirable side effects (1) the most common and most dreaded being a reduced resistance to bacterial viral arly herpetic) and mycotic infections 30% of posttransplantation deaths are due to complications (2) In our 29 cases more or less pronounced signs of an inflammatory process were present in 27 smears mycotic infections predominating with an incidence of 15 This compares with an incidence of only 9% in the total population of our department Trichomonas normally among the most common organism encountered in the vagina was present in only 1 case In another case vulvar vaginal and perianal condylomata acuminata were seen This is apparently suggestive of a viral infection

The mutagenic and oncogenic potential of cytostatic substances such as used for immunosuppressive therapy is well documented Alkylating agents are for instance known to have a carcinogenic effect This is explainable by tl terfering with the synthesis and/or struct nucleic acids A potential carcinogeni ar antibiotics and antimetabolites is discussed (3

Aside from the direct cellular effe ts i munosuppressive agents the reduced immu cal response to spontaneous mutations a cogenic viruses as well as the continuou genic stimulation of the RES by allografts vs host reaction) may be factors und the accumulated incidence of tumors munosuppressed patients (6) All of thes may potentiate the effects of known carcin agents (7) Taken individually a single thera modality is thus not very likely to incre cancer hazard But immunosuppressive thera collectively been incriminated as a factor u ing the reduced response of the organism to c i e the immuno surveillance (8) Pretrans tion suppression of immunologic responses

reuremic condition of renal transplant recipi nay be a compounding factor (9)

immunosuppressed patients the risk of de ing cancer is 50 to 100 times higher than in an ated group of comparable age Enderlin & in (6) found 3 tumors (4 6%) in 65 transplant ents of the 352 renal transplant cases ated by Penn & Starzl (7) 17 had tumors 6) When excluding those patients who had by the 4th postoperative month the figures are and 5 6% respectively Correcting their fig for non survivors Wegmann et al (9) found le novo tumors in 190 cases The incidence ted by Birkeland & Kemp (10) in a material of cases was however only 0 75% In a control le of comparable age by contrast the inci e was no more than 0 058% (7)

the de novo tumors 62% are epithelial and mesenchymal Sarcomas of the lymphoreticu ystem (29%) are significantly common about of them localize in the CNS and the spinal d Skin and lip tumors equally account for

ie average age of patients with epithelial tumors years) is higher than for mesenchymal tumors ears) Mesenchymal tumors are found to occur er after transplantation (22 months) than epi al tumors (33 months following the transplanta on an average) Unlike mesenchymal tumors inomas localizing at the body surface have a d prognosis (11)

he first cervical carcinoma following a kidney splantation was reported by Tallent et al in l (12) Since that time the Denver transplan on center alone had registered 18 cervical inomas by March 1974 These account for 8% ll de novo tumors recorded Of the Denver s 16 were preinvasive and 2 were invasive patients age was 22 to 50 years (mean 36 rs) the posttransplantation interval being 6 to 97 ths (mean 38 months) Pretransplantation ology had only been done in 5 cases all of them ig negative Statistical computation showed that iunosuppressed patients are 14 times more ly to develop carcinoma of the cervix (13) than rs

i our material of 29 female renal transplant reci its ? had squamous dysplasia of the cervix hough in one case the excision of the dysplastic helium had extended far into intact tissue sub- uent smears failed to be negative Post conization colposcopies again revealed iodine nega tive areas of variable dimensions and focal leuko plakia On cytology atypical cells were again seen The disseminated occurrence of areas of atypical epithelium might suggest that in association with reduced immune response these changes develop not only at the squamo-columnar junction but also at multiple sites of cervix and vagina

While carcinoma of the cervix has repeatedly been reported to develop in immunosuppressed pa tients the literature available to us lists only 1 case of posttransplantation endometrial carcinoma (14) The case presented by us appears to be of particular interest as the curettage performed 1 year prior to the diagnosis of endometrial carcinoma had been negative

Both the reports in the literature and our own observations document the need for gynecological and cytological follow up studies at short intervals in all females undergoing immunosuppressive therapy after organ transplantation These follow up studies at an interval of 6 months usually help to detect premalignant or early malignant growths in the genital tract at a time at which these can readily be treated without discontinuing immunosuppres sive therapy

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Submitted for publication Nov 3 1976

H Husslein
II Universitats Frauenklinik
Spitalgasse 23
1090 Vienna
Austria

Acta Obstet Gynecol Scand 57 79–83 1978

REGRESSION OF TUMOUR GROWTH AFTER ADMINISTRATION OF ALKOXYGLYCEROLS

Astrid Brohult Johan Brohult and Sven Brohult

n Radiumhemmet Karolinska sjukhuset Stockholm 60 Medical Department IV Sodersjukhuset Stockholm 38 and the Royal Academy of Engineering Sciences Stockholm Sweden

act A regression of tumour growth is observed ı alkoxyglycerols are administered prior to radiation ment of patients suffering from cancer of the uterine x This regression has been demonstrated by a ge in the quotient between the incidence of early and nced stages

ıxyglycerols occur in small quantities in many ral products In the haemopoietic organs of ımals particularly the bone marrow they are ıvely abundant They are also found in rela y high concentrations in human mother s milk / occur most abundantly in nature in the liver f certain species of shark (1 8 9) The general ula for alkoxyglycerols is CH_2OH CHOH O R where R is a long chain aliphatic radical ıe alkoxyglycerols have proved to be of medi ınterest (1–7) To some extent they prevent ɔpenia and thrombocytopenia The administra of alkoxyglycerols before during and after ıtion treatment of patients with cancer of the ne cervix results in higher survival rates than if ıtion treatment alone is given (1 2) Further the alkoxyglycerols promote the growth of *ɔbacillus lactis* (1) the formation of antibodies *) and they reduce to a large extent (ca 50%)* equency of injuries following radiation therapy 10)

e aim with the present study has been to in gate the regression of tumour growth when yglycerols are administered before radiation ment of patients suffering from cancer of the ıe cervix

MATERIALS AND METHODS

linical experiments in this study were conducted alkoxyglycerol preparations from the liver oil of the Greenland shark The preparation produced by AB Astra with the working name AT 18 is a concentrate containing 85% free alkoxyglycerols The contents of various alkoxyglycerols from a variety of sources are given in Table I

The alkoxyglycerols were administered orally in capsules 2 capsules 3 times a day each capsule containing 0 1 g of alkoxyglycerols The total daily dose thus was 0 6 g

The practical procedure was as follows Immediately upon the receipt of the referral letter the patient was given a date for the commencement of radiotherapy and at the same time a package containing the alkoxyglycerols and information regarding the dosage At the start of

Table I *Percentage composition (weight) of alkoxyglycerols from various sources*

Alkoxy glycerols	Human bone marrow	Human milk	Liver oil Greenland shark
14 0			2 0
15			0 7
16 0	29 4	23 9	9 1
16 1		trace	10 8
17	7 6	3 6	3 6
18 0	4 6	22 8	2 8
18 1	16 7	33 8	59 4
18 2		1 4	1 6
18 3			
19*	6 1	2 4	1 5
20 0	2 9	1 6	
20 1	3 2	2 3	6 2
22 0	0 7	0 7	
22 1	5 1	3 4	2 2
24		2 1	

Analyses are according to Hallgren & Larsson (? 3)
The number of carbon atoms in the first column refers to the long-chain component of the molecule The number after the colon denotes the number of double bonds

Both branched and normal chains C_{15} C_{17} and C are present

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Submitted for publication Nov 3 1976

H Husslein
II Universitäts Frauenklinik
Spitalgasse 23
1090 Vienna
Austria

le IV *Distribution according to clinical stages (1958–1975) Stage I A excluded*

	I B		II A		II B		III		IV		I B–IV
	n	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*
adiotherapy											
–64	646	25 1	806	31 3	564	21 9	384	14 9	176	6 8	2 576
–75	393	27 1	408	28 1	329	22 7	225	15 5	95	6 6	1 450
ıl	1 039	25 8	1 214	30 2	893	22 2	609	15 1	271	6 7	4 026
rophylactic administration of alkoxyglycerols											
od 1	159	38 5	129	31 2	71	17 2	39	9 5	15	3 6	413
od 2	36	30 0	39	32 5	19	15 8	18	15 0	8	6 7	120
od 3	84	36 7	78	34 1	34	14 8	26	11 3	7	3 1	229
ıl	279	36 6	246	32 3	124	16 3	83	10 9	30	3 9	762

le V A *Decrease in advanced stages after prophylactic administration of alkoxyglycerols (all stages)*

p	No of patients	E *n*	E %	A *n*	A %	E/A	D (%)	D_A (%)
otherapy 8–75)	4 400	2 627	59 7	1 773	40 3	1 48	12 1	30 0
hylactic administration ods 1 2 3)	840	603	71 8	237	28 2	2 54		

A+I B+II A A=II B+III+IV D=Decrease in per cent D_A=Decrease in per cent related to the number of its with advanced stages

e V B *Decrease in advanced stages after prophylactic administration of alkoxyglycerols (Stage I A ıded)*

B+II A A=II B+III+IV

	No of patients	E *n*	E %	A *n*	A %	E/A	D (%)	D (%)
therapy 3–75)	4 0?6	2 253	56 0	1 773	44 0	1 27	1? 9	29 3
ylactic administration ods 1 ? 3)	762	525	68 9	237	31 1	2 22		

a numerical evaluation of the shift in stage ıving prophylactic administration of alkoxygly ıt is convenient to subdivide the stages into ıced stages A=stage II B and higher and early E=II A and lower Based upon bimanual tion the referral of patients to group A or E is with a high degree of accuracy while the ntiation between other stages often presents ılties The distribution of A and E (E_1=I A+I B+II A and E_2=I B+II A) for the different groups is given in Table V The decrease in the advanced stages (D) after prophylactic administration is statistically significant ($P<0$ 001)

The percentage of early and advanced stages is given for each year during 1958–75 (Table VI) No systematic change with time is observed for the years when the patients were treated with radiotherapy but did not receive alkoxyglycerols pro-

Table VI *Distribution of early and advanced stages (1958–75)*

	Year	No of pats	E_1 I A+I B+II A *n*	%	A II B+III+IV *n*	%	E_1/A	No of pats	E_2 I B+II A *n*	%	A II B+III+IV *n*	%
	1958	428	251	58 6	177	41 4	1 42	419	247	57 8	177	42.2
	1959	436	251	57 6	185	42 4	1 36	410	225	54 9	185	45 1
	1960	356	201	56 5	155	43 5	1 30	336	181	53 9	155	46.1
	1961	401	236	58 9	165	41 1	1 43	379	214	56 5	165	43.5
	1962	426	261	61.3	165	38 7	1 58	388	223	57 5	165	42.5
	1963	348	225	64 7	123	35 3	1 83	307	184	59 9	123	40 1
	1964	381	227	59 6	154	40 4	1 47	337	183	54 3	154	45 7
Period 1	*1965*	458	333	*72 7*	125	*27.3*	*2 66*	413	288	*69 7*	125	*30.3*
	1966	309	190	61 5	119	38 5	1 60	266	147	55.3	119	44 7
	1967	318	200	62 9	118	37 1	1 69	285	167	58 6	118	41 4
	1968	299	171	57 2	128	42 8	1 34	279	151	54 1	128	45 9
	1969	290	168	57 9	122	42 1	1 38	259	137	57 9	122	47 1
Period 2	*1970–1972*	137	92	*67.2*	45	*32.8*	*2 04*	120	75	*62.5*	45	*37.5*
	1970–1972	142	88	62 0	54	38 0	1 63	125	71	56 8	54	43.2
Period 3	*1973–1975*	245	178	*72 6*	67	*27 4*	*2 66*	229	163	*70.7*	67	*29.3*
	1973–1975	266	158	59 4	108	40 6	1 46	236	178	54 2	108	45 8

phylactically A shift towards earlier stages occurs however for the periods 1 2 3 (prophylactic administration of alkoxyglycerols)

COMMENTS

The regression of tumour growth demonstrated by a change in the quotient between early and advanced stages is observed as a consequence of administration of alkoxyglycerols prior to the radiation treatment It is of importance to mention that regression is due to a non toxic natural substance found in the human body (1) Furthermore the incidence of injuries following radiation therapy is markedly reduced by the administration of alkoxyglycerols Complex injuries (due to radiation injury and tumour growth in combination) are reduced to about 1/3 in a group receiving alkoxyglycerols in prophylactic administration A more detailed analysis of the effect of alkoxyglycerols on the incidence of injuries is published elsewhere (7)

The regression of tumour growth and the decrease in injuries following radiotherapy influences the survival rate This dependence will be discussed in a separate paper (6)

It is evident that there are prospects of improving the effect of alkoxyglycerol therapy Seven days of prophylactic administration of alkoxyglycerols results in a marked reduction of the advanced stages 12–13% (30% if the decrease is related to number of patients with advanced stages Tab It would be worthwhile carrying out clinical with a patient group receiving proph administration of alkoxyglycerols dur weeks Furthermore some observations that a prolonged administration of alkoxygl after radiotherapy might be of value

ACKNOWLEDGEMENTS

This work was supported by grants from the K Alice Wallenberg Foundation and from the S Dagmar Salen Foundation

We wish to thank Prof H L Kottmeier and Tjernberg former and present head of the Depar Gynaecology of Radiumhemmet Stockholm for discussions Our thanks are also due to Prof Joelsson for stimulating criticism and advice

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Submitted for publication May 16 1977

Astrid Brohult
Radiumhemmet
Karolinska sjukhuset
Stockholm 60
Sweden

ANNOUNCEMENT

The 6th European Congress of Perinatal Medicine is being held in Vienna Austria August 30–September 1 19

Information on the congress as well as programs may be obtained from the secretariat Interconvention Ka gasse 5 A 1095 Vienna Austria

Acta Obstet Gynecol Scand 57 85–88 1978

IMMUNOCHEMOTHERAPY IN ADENOCARCINOMA OF THE OVARY

P K Kalpaktsoglou G B Ioannidou A P Kondyli S I Lekou
D Papaconstantinou and A C Comninos

From the Immunobiology Research Centre Marika Eliadi Maternity Hospital Athens Greece

ract Immunochemotherapy combined with total erectomy was used in the treatment of 21 cases of iocarcinoma of the ovary of which 7 were in stages Ib 8 in stage III and 6 in stage IV Another 6 cases had liation with or without hysterectomy or various other mes of treatment prior to immunochemotherapy The unotherapy depends on stimulation of the humoral cellular immunity by a battery of antigens (Te Di–Te ienza mumps) Chemotherapy starts by administra of cyclophosphamide three days after each course of unotherapy Each course of immunochemotherapy is wed by a period of 10 days free from any medication stimulation of the immune mechanism with B C G s 10 days after the 4th course of immunochemo- apy This last course of treatment is repeated up to the of the first year of immunochemotherapy The same ial scheme of treatment is constantly repeated The nts are under constant clinical and laboratory w up The cyclophosphamide is discontinued when the WBC falls below 4500 to 4000 per cmm All nts receive vitamins A E C and B complex All our s of stages Ic–IIb and III with total hysterectomy without any prior treatment showed a progressive very and are living normal lives The lymphocytes mmunoglobulins and the E rosettes returned in most ir cases to normal levels The favourable results and urvival rate obtained in cases of cancer without dis metastasis may be attributed to the reduction of the ur masses by surgery to the administration of ens prior to chemotherapy which seems to diminish ide effects of cyclophosphamide to the administra of cyclophosphamide in small daily doses to avoid ɔpenia and finally to the fact that patients are under inuous protective immunochemotherapy

revious studies we have shown that combined unotherapy and chemotherapy in mice with splantable myeloma tumour (3) or spontaneous imary carcinoma (4 6 9) decreases the mortal ate Also immunochemotherapy in carcinoma ie reproductive system of the human female results in a rapid amelioration of the patient s general condition and a prolonged recovery (1 7 8 9)

The purpose of our present study is to present the results obtained by immunochemotherapy in cases of adenocarcinoma of the ovary stages Ic–IIb III and IV (F I G O)

MATERIAL AND METHODS

Scheme of treatment The scheme of treatment is divided into two parts First the stimulation of humoral immunity by a battery of antigens in four consecutive courses of treatment and second the stimulation of cellular immunity by B C G antigen administered orally

Fig 1 shows the scheme of treatment applied The active nonspecific humoral immunization is divided into four consecutive courses In the first course we administer tetanus antigen (Te 1 ml S C) in the second diphtheria —Te (Di–Te 1 ml S C) in the 3rd Di–Te and three days later influenza antigen in the 4th course Di–Te three days later influenza and after another three days mumps *antigen*

Chemotherapy starts three days after each course of immunotherapy with administration of cyclophosphamide in a total dose of 60 mg/kg I V (stages III and IV) or 30 mg/kg (stages Ic–IIb) per course of treatment divided into daily doses not exceeding 200 mg A period of 10 days free from any medication is always left between the courses of immunochemotherapy

The stimulation of cellular immunity starts 10 days after the 4th course of immunochemotherapy We administer 10 mg of B C G orally every second day up to the total dose of 60 mg After three days free from medication the patient receives daily 50 mg of cyclophosphamide orally for 10 to 15 days This last course of treatment is repeated up to the end of the first year of immunochemotherapy with intervals of 10 days free from any medication between each course of treatment The same annual scheme of treatment is repeated with the only difference that cyclophosphamide is administered orally and in a daily dose of 50 mg for 10 days

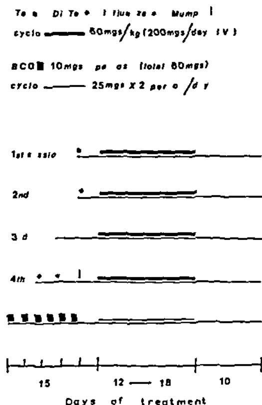


Fig 1 Scheme of immunochemotherapy

During the first four courses of treatment the patients undergo a check up every 5 to 10 days which includes WBC Ht platelet count *determination of serum levels of* the immunoglobulins G A and M and the NBT positive cells by a modified method (5) Since the beginning of 1975 we have also studied by a micromethod (10) the number of spontaneous E rosettes in the peripheral blood before and again before every second course of im herapy

The administration of cyclophosphamide is discon whenever the WBC falls below 4 500 to 4 000 per mm³ Antibiotics are administered whenever the NBT positive cells exceed the absolute number of 1 200 per mm³ or the percentage of 20

All patients are under continuous vitamins A E B complex and C treatment

The above scheme of treatment has been combined with total hysterectomy in 21 cases of adenocarcinoma of the ovary of which cases 7 were in stages Ic–IIb 8 in stage III and 6 in stage IV None had any other prior treatment We have also treated another 6 cases 3 in stage III (one with prior irradiation and two without total hysterectomy) and *3 in stage IV with various prior schemes of treatment and* surgery

RESULTS

All but one of our cases of stages Ic–IIb and III with hysterectomy showed satisfactory recovery The exception is a patient who 22 months after beginning of treatment had partial intestinal struction All cases in stage IV had an initial pe of 2 to 4 months of moderate recovery relapse and a survival rate not exceeding 7 mo

Fig 2 shows the survival rate of cases of Ic–IIb and III As shown in this figure all ou treated by total hysterectomy showed sa recovery and live normal lives Two cases of III without hysterectomy died the one 1? and the other 25 months after treatment st

Fig 3 shows the serum levels of the im*noglobulins G A and M in I U /ml just be* treatment The immunoglobulin G in normal viduals ranges between 90 and 140 I U /ml between 100 and 180 I U /ml and IgM between and 240 I U /ml As shown in Fig 3 cases of IV show levels of IgG below 80 I U /ml (3 ca IgA above 250 I U /ml (one case) and IgM be 100 I U /ml (3 cases) In cases of stages Ic–II III the immunoglobulins remain or return levels during the whole period of treatment

Fig 4 shows the absolute number and percentage of circulating lymphocytes *just be* the beginning of non specific humoral (Te₁) and before the beginning of non lar immunization (B C G ₁) in cases of stages and III The absolute number of ly *shows a drop in* all cases This drop is related to the decrease in the number of cir

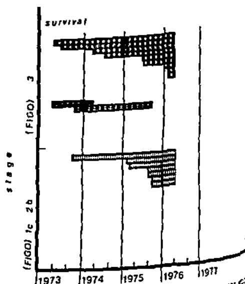
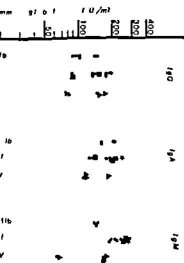


Fig 2 Length of survival of the cases 7 cases Ic–IIb (▭) 9 cases stage III with hysterectomy cases stage III without hysterectomy (▦)



Serum levels of the immunoglobulins G A and M
efore treatment in cases with hysterectomy and
t any prior treatment (●) with hysterectomy and
rradiation (*) without hysterectomy and without
reatment (■) with prior multiple schemes of treat
nd surgery (▲)

cytes which ranged between 7000 and 12000/
before treatment (Te_1) and between 6000 and
/mm³ before the beginning of B C G $_1$ The
ntage of lymphocytes increases in most of the
of stages Ic–IIb and decreases in cases of
III

5 shows the absolute number and the
ntage of the spontaneous E rosettes In nor
individuals the absolute number and the
entage of E rosettes range between 100 and
nm³ and 7 and 20% respectively Out of the 6
of stages Ic–IIb studied only two show low
ute numbers and low percentages just before
beginning of immunochemotherapy (Te_1) In
cases the E rosettes show a significant rise
e the beginning of B C G $_1$ in two they remain
anged and in one a significant drop is noted In
latter case the absolute number and the
entage of E rosettes have returned to normal
s two months later Out of 5 cases of stage III
showed an absolute number of E rosettes
w 100/mm³ and a percentage below 5 before
treatment In four of these cases the absolute
ber and the percentage of E rosettes returned to
al levels just before the beginning of B C G $_1$
n one case two months later

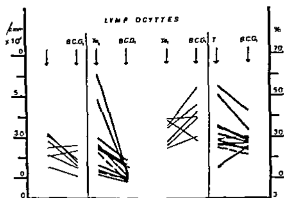


Fig 4 Absolute number and percentage of circulating lymphocytes just before the beginning of non specific humoral immunization (Te_1) and before the beginning of non specific cellular immunization (B C G $_1$) cases of stages Ic–IIb (—) cases of stage III with hysterectomy (—) cases of stage III without hysterectomy ( )

DISCUSSION

Since 1973 we have used a scheme of immunochemotherapy in cases of adenocarcinoma of the ovary

Immunotherapy preceding chemotherapy seems to diminish the side effects of cyclophosphamide and to protect the patients lymphohaemopoietic tissues By administering cyclophosphamide in a small daily dose and in consecutive courses of treatment with intervals of at least 10 days free from any medication we provide the period of time necessary for most of the tissues to return to their normal structure and function We thus try to restrict the

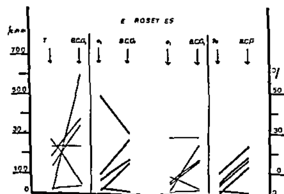


Fig 5 Absolute number and percentage of spontaneous E rosettes cases of stages Ic–IIb (—) cases of stage III with hysterectomy (—) cases of stage III without hysterectomy ( )

uptake of cyclophosphamide to the malignant cells and protect all tissues from irreversible damage

The favourable results obtained in our cases of cancer without distant metastasis may be attributed to the fact that the patients are under continuous protective immunochemotherapy

The effect of the treatment applied depends on the extent of the masses of the malignant cells We therefore recommend surgery even in advanced cases with the intention to reduce the tumour masses as much as possible

We start our treatment by applying a non specific humoral immunization with the aim to stimulate T cells and macrophages participating in the humoral immune response in order to trigger indirectly the cellular immunity which is very often affected

The study of the spontaneous E rosettes constitutes the proof that our efforts have been successful as in most of our cases the percentage and the absolute number of E rosettes increased after the first or second active non specific humoral immunization

In the cases of stages Ic–IIb the absolute number of circulating lymphocytes shows a drop while their percentage remains either unchanged or is increased In the cases of stage III both absolute number and percentage of circulating lymphocytes are reduced As an increase of E rosettes has been observed in most of our cases, we suspect that the reduction of circulating lymphocytes may be associated with their removal from the circulation and their concentration at the tumour rejection area

The levels of the serum immunoglobulins may ...ort the view that immunoglobulin G is rarely ...cted while on the contrary high levels of IgA ...d low levels of IgM often coincide with a poor prognosis This finding has also been observed in experimental animals (6 9)

Abnormal levels of serum IgG or IgA return very often to the normal values with the progress of the treatment while low levels of IgM rarely do so

In the cases of stage IV the scheme of treatment applied is followed by a short lasting (2 to 4 months) recovery In this stage of the disease the unsatisfactory results may be attributed to a blockage of the immune system which is unable to respond to any antigen

On the other hand in cases of adenocarcinoma stages Ic–IIb and III the therapeutic effect is excellent followed by a prolonged recovery and a significant increase in the survival rate

ACKNOWLEDGEMENTS

This research work has been supported by ... search Foundation Athens/Greece Grant 1010 ... Wellcome Trust London Grant BECH/EM P.30

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Submitted for publication Nov 12 1976

A C Comninos
Marika Eliadi Maternity Hospital
Elena Venizelos Foundation
20 Kanari Street
Athens 138
Greece

Acta Obstet Gynecol Scand 57 89–94 1978

VAGINAL AGENESIS

An Analysis of Ninety Cases

Carlos Alberto Salvatore and Orlando Lodovicci

*From the Gynecology Clinic of the University of Sao Paulo Medical School
Sao Paulo Brasil*

tract This study of 90 cases of vaginal agenesia wed the following results 50% of the patients sought lical advice when between 16 and 20 years of age 1% of the patients were not married amenorrhea was sent in 100% of the cases with hypogastric pains in ¢ the uterus was not palpable clinically in 77 7% of cases 77 7% of the patients had total agenesis 11 1% partial agenesis and 7 7% had hematometra ough laparotomy 75 5% were found to have normal ries 92 5% of the cases were histologically normal arotomy showed the uterus as solid rudimentary in 5% of the cases and absence of the uterus in 24 4% of cases the Fallopian tubes were normal in 32 22% of cases and rudimentary in 46 6% excretion urography closed renal anomalies in 17 5% surgical treatment by McIndoe technique carried out in 90 cases gave 5% satisfactory results the follow up made between and 5 years in which the long term use of an acrylic uld is recommended in those who do not have sexual tions showed permanence of the satisfactory results 1 3% of the cases of which 83 3% were after one ration only neovaginal cytology done between one 6 years showed 72 2% of the cases with acidophyl s between 5 and 20% with acidophily between 21 and

ginal agenesis is a legal social and medical prob of great importance demanding treatment at right period of the woman s sexual evolution It malformation that sometimes goes unnoticed up the time of puberty when it is realized that nstruation has failed to appear

Vaginal agenesis is a result of arrested develop nt of the Mullerian ducts hence its frequent ociation with uterine aplasia According to most hors (e g 2 9 12) the external genital organs e a normal appearance with or without the pres e of the hymenal membrane and a small de ssion where the vaginal opening should be

Vaginal agenesis is easily diagnosed and is sel n connected with the form of intersexuality as iated with sex chromosome abnormalities It is frequently associated with changes in the urinary system

Surgery is the treatment that offers the best re sults demonstrated in the practice of neovagino plasty according to McIndoe (2) but the time of the woman s reproduction life at which its should be carried out is still under discussion Williams (21) recent technique prepares the neovagina in a situa tion unfavourable for coitus Consequently we are still using the McIndoe operation

In previous works (17 18) it was shown that according to several authors neovaginoplasty is in dicated immediately when there is hematometra and in those patients who have attempted sexual in tercourse (1 2 5 13 15)

We have reported previously 2 patients with hematometra and 18 who have tried to accomplish coitus of whom 16 were married Generally speak ing however neovaginoplasty must be done in cases where the wedding is imminent and accord ing to the case after 17 years of age so as to facilitate the integral development of the personali ty If the operation is performed—sometimes be fore intercourse is likely to occur—there is an in creased risk of stenosis of the neovagina

The methods used in the making of an artificial vagina were reported at length in a previous work in which we studied 42 cases (17) and in which we stressed the efficacy of the McIndoe method

In the present study we report a total review of the cases we have treated including those quoted previously and those reported by Lodovicci (10)

METHOD AND MATERIAL

Our series consists of 90 cases observed at the Gynecologic Clinic of the University of Sao Paulo Medical School The patients underwent a gynecological examina

tion (rectal palpation under narcosis) laparotomy (36 cases) or laparoscopy (54 cases) excretion urography (40 cases) and determination of genetic sex (40 cases)

The operating technique is as follows (19) The patient must be placed in a semigynecological position We prefer the McIndoe technique for the building of the neovagina using a free skin graft taken from the abdomen The opera tion has two fundamental parts the preparation of the graft followed by construction of the tunnel between the rectum and the urethra and bladder We usually operate together with a plastic surgeon

The abdominal stage

After preparing the abdominal skin the plastic surgeon takes a skin layer with the dermatome big enough to cover the acrylic mould The raw part of the abdomen is protected with gauze and cotton and bandaged The plas tic surgeon then prepares the mounting of the epidermis over the acrylic mould sewing the edges with nylon thread while the gynecologist prepares the neovaginal tunnel

The vaginal stage

An incision is made with the scalpel transverse to the vestibule or to the retrohymenal fossette between the anus and the urethral meatus One tries to cut first trans versely the bundles of the fibrous perineal nucleus found between the urethra and the anus-rectum The inci sion is deepened and two small tunnels are formed on either side of the urethra These are subsequently united in the mid line By means of the scalpel or its handle or else with curved tip scissors the urethra and bladder are separated from the rectum up to the point where the base of the peritoneal bladder-rectal sac is reached In this stage of the procedure we never open the urethra the bladder or the rectum—an accident which often happens when the surgeon attempts to advance the dissection through the mid line The tunnel must be large enough to a medium sized acrylic mould Absolute haemostasis l small vessels is obtained with plain catgut number 00

According to the case a partial dissection should be done at the sides of the pillars of the elevator ani muscle so as to avoid subsequent stenosis of the vaginal introitus

After the mould is prepared and haemostasis is con firmed and after the tunnel has been soaked with physiological serum the acrylic mould covered with the epidermis taken from the abdomen is introduced

The mould is fixed with cloth bandages passing through the mould s screw and attached to the abdominal bandages with sticking plaster

The patient must remain in bed until the seventh or eighth day when she is allowed to walk and to take out the mould She must subsequently undergo re dressing every 48 hours the mould being removed and re inserted She must be instructed concerning the long term hygiene of the neovagina in order to avoid stenosis Details of the post opreative management are to be found in other papers (10 17)

An acrylic mould is inserted soon after surgery and it remains in place for 8 days The dressing is changed every other day and after discharge about the 14th day the patient herself will prepare and apply the dressing, consisting of removing and reinsetting the mould into the neovagina over a period of 6 months

ANALYSIS OF THE MATERIAL

Age (90 cases of vaginal agenesis)
10-15 years 7 cases
16-20 years 46 cases (50%)
21-25 years 24 cases
26-30 years 10 cases
31-35 years 4 cases

Civil status
Unmarried 64 cases (71 1%)
Married 26 cases (28 9%)

Symptoms
Amenorrhea 90 cases (100%)
Impossibility of coitus 22 cases (24 4%)
Hypogastric pain 18 cases (20%)

Gynecological examination (Rectal)
Non palpable uterus 70 cases (77 7%)
Rudimentary palpable uterus 14 cases
Uterus increased in volume 4 cases
unrecognizable ovaries 80 cases (88 8%)
Palpable ovaries 8 cases

Diagnosis
Total agenesis 70 cases (77 7%)
Partial agenesis 10 cases (11 1%)
Male pseudo-hermaphroditism 3 cases
Total agenesis plus haematometra 3 cases (7 7%)
Partial agenesis haematometra and haema. 2 cases (7 7%)
Total agenesis haematometra and haema osalpinx 2 cases (7 7%)

Internal genital organs observed through Laparoscopy (54 cases) and Laparotomy (36 cases)
(*a*) Ovaries
Normal 68 cases (75 5%)
Polycystic 6 cases
Hypoplastic 12 cases
Rudimentary 4 cases
(*b*) Histology of the gonads (biopsy) (40 cases)
Normal ovaries 37 cases (92 5%)
Rudimentary testicles 3 cases
(*c*) Uterus
Hypoplastic 2 cases
Increased in volume (haematometra) 4 cases
Solid rudimentary 50 cases (55 5%)
Double uterus 1 case
Bicornuate uterus 3 cases
Hemi uterus 4 cases
Two rudimentary uteri 4 cases
Lack of uterus 22 cases (24 4%)
(*d*) Tubes
Normal 29 cases (32 2%)



Fig 1 Collin speculum in the neovagina

ioplastic 6 cases
imentary (long) 42 cases (46 6%)
rudimentary tube 2 cases
k of tubes 10 cases
natosalpinx 1 case

reting urography (40 cases)
ters and normal kidneys 33 cases (8? 5%)
ible pelvis–calyces 3 cases
k of left kidney 4 cases

etic sex (40 cases)
ence of the female sexual *chromatin* 36 cases
k of the female sexual *chromatin* (male) 4 cases

itment (90 cases)
al neovagina 80 cases (88 8%)
ial neovagina 10 cases
ivagina and draining of the haematometra through the agina 3 cases
ial neovagina and draining of the haematometra and aematocolpos (through the vagina) 2 cases
vagina and draining of the haematometra through the bdomen (hysterotomy) 1 case
vagina and draining of the haematometra and aematosalpinx (through the abdomen) 1 case
vagina and clitoris amputation 2 cases

ilts (90 cases)
od graft integration and good vaginal permeability 75 ses (83 3%)
inal stenosis (fibrous ring) (2 re-operated with tisfactory results) 9 cases
ial disintegration of the graft due to a haematoma (all -operated with satisfactory results) 6 cases
il satisfactory results including the 5 who were re berated 81 cases (90 0%)

Follow up (between 1 and 6 years) (70 cases)
Good results (penetration of the Collins speculum medium sized) (Figs 1 2) 64 cases (91 3%)
Partial stenosis 6 cases
With normal sexual relations 54 cases
With dyspareunia 4 cases
With normal menses 4 cases
Pregnancies (caesarean) 2 cases

Cytology of neovagina (25 cases)
(between 1–6) (Fig 3)
From 5 to 20% of acidophil cells 18 cases (72 0%)
From 21 to 40% of acidophil cells 7 cases (28 0%)
Biopsy of the neovagina showed atrophic epidermis (Fig 4)

COMMENTARY

As may be observed from an analysis of the cases most patients sought advice in the age range 16 to 20 years (50% of the cases) coinciding with a wait of 3–5 years for the onset of the menarche As a matter of fact primary amenorrhea was the predominant symptom (100% of the cases) Hypogastric pains occurred in 20% of the cases and attempts at sexual intercourse among those who had tried had been unsuccessful in around 24 4% of the cases

Of the cases examined 28 9% of the patients were married and had serious problems just after the marriage Because of such problems most authors think that the ideal age for the making of the neovagina is before the marriage As we have stated



Fig 2 Collin speculum in the neovagina (cul-de sac)

in an earlier work (18) libido was present in 79 1% of the 49 cases previously studied

The diagnosis of vaginal agenesis is an easy one The gynecological examination by rectal palpation allows the non identification of the uterus in 77 5% of the cases Moreover 77 7% of our 90 cases were of total vaginal agenesis and 11 1% of partial agenesis There was haematometra in 7 cases (7 7%)

The exploration of the internal genitalia by means of laparoscopy and laparotomy is unavoidable but shows that the ovaries are normal in 75 5% of the cases In 3 of the cases (pseudo hermaphrodite the biopsy revealed rudimentary testicles confirmed by histological study The psychological analysis in these cases was more important than analysis of the sexual chromatin—hence th indication for a neovagina

A solid rudimentary uterus was found in 55.5% of the cases lack of uterus in 24 4% and functional uterus with haematometra in only 7 cases (7 7 These results agree with those of Counseller (



Fig 3 Acidophil cells of the neovagina



Fig 4 Atrophic epidermis in the neovagina 3 years after the operation

76) of Bryan et al (2) (4 in a 100) Jackson (7) (5 128) Cordier (4) (1 in 23) Lodovici (10) (1 in 16) l Jeffcoate (8) These findings indicate its ex nce in 10% of cases Normal tubes were in the ne way found in only 32 2% of the cases

The practice of excretion urography is an im tant one as was shown by us and several other hors The frequency of malformation of the uri y system is very high in cases of vaginal nesis Thus the absence of one of the kidneys (4 es) and double pelvis-calyces (2 cases) was erved in 17 5% of the cases In a previous work an analysis of 21 cases 15 (71 4%) were normal l the rest (28 6%) showed anomalies of the uri y system as represented by the lack of one of the neys dilation of the ureters of pelvis double ters anomalous implantations rotation dis cement of one of the kidneys or dislocated ney thus confirming the reports of others (5 7

n the experience of many authors (5 7 9 10 13 17 18) the choice of treatment is the making the neovagina by the McIndoe technique— Indoe having in 1950–59 established the basic nciples for the formation of the neovagina from skin grafts

ighty complete neovaginas were made (88 8%) l 10 partial ones i e the vagina was completed in se cases where the agenesis was partial In two hese cases there was agenesis of the exterior half of the vagina the inner half being full of menstrual blood (haematocolpos) The remaining 7 cases showed the presence of a vagina in its exterior third In the 6 patients who had a functioning uterus perforated moulds were used

As we have stated in a previous work (18) we recommend the use of an acrylic mould by the patient until the beginning of regular sexual activity returning to its use in cases where a long interruption occurs

The results of the McIndoe technique are good as graft integration occurred in 83 3% of the cases If we add 6 cases where the integration was partial but re operation was necessary we achieved 90% of optimum graft integration and optimum conditions of permeability We observed the presence of a fibrous ring in only 9 of the 90 cases Page & Owley (14) claim 81% good results

The late follow up observed between one and six years showed 91 3% satisfactory results in 70 cases of which 54 had normal sexual relations two had become pregnant and undergone caesarian section Only 6 cases showed a small vaginal stenosis and 4 complained of dyspareunia We have not so far found enterocele

In our experience therefore the McIndoe technique for the making of an artificial vagina is the one offering the best results and the long term use of an acrylic mould guarantees the late success of the operation

stenosis of the introitus occurred in three patients Our best results were obtained with ambulant dilatation

Can women also conceive if they have their uterus? Four patients had an uterus present In two the cervix was absent and the uterus was removed early in the operation We sewed the two other uteri into the neovagina The women had regular menstruation but they did not conceive After six years we removed the uterus in one of them because of endometriosis

The same technique can also be applied at the end of Wertheim s operation when the greater part of the vagina is removed and if the patient is young and wishes it The purpose is the same as in the cases of congenital aplasia of vagina to make sexual intercourse possible and in this way to alleviate the physical and psychological deficiency of these women

The reconstruction of the vagina after Wertheim s operation consists in lengthening the vagina which remains after the operation with a short segment of the colon that we resect from the sigmoid The technique of this operation is accurately described by L Kos in his thesis (6)

For reconstruction after the Wertheim operation only a 5 to 6 cm length of sigmoid is sufficient It is easily displaced downwards to the level of the remaining vagina without having to resect any sigmoid artery This has several advantages the neovagina is well supplied with blood and there is no risk of necroses As we do not loose time with ligating the sigmoid arteries the reconstruction only takes half an hour at the most

We form the neovagina by closing the resected sigmoid segment at one end and bringing the other end near the hinder part of vagina in order to perform the colovaginal anastomosis The cupola of the neovagina can be either the proximal or distal end of the resected segment It does not matter in which direction peristaltic action occurs As a matter of fact we perform the anastomosis with that end of the resected sigmoid that can be most easily brought to the hinder part of vagina However this depends on the anatomy of sigmoidal arteries as well as on origin of the mesosigmoid

In most cases the lumen of the hinder part of vagina and the sigmoid are not of the same size usually the lumen of the sigmoid is narrower It must be enlarged before suturing the colovaginal anastomosis This is performed by splitting it along the taenia for 2 cm or more if necessary in order to make both lumina approximately the same size By this simple act the formation of stenoses at the colovaginal anastomosis is prevented Our experience has also been that silk is most appropriate for suturing the colovaginal anastomosis The stitches must not be made too closely three stitches in front and three behind are sufficient

In reconstructions performed at the same time as the Wertheim operation we had no deaths We had one rectovaginal fistula which closed spontaneously after temporary colostomy and one abscess which drained the the colovaginal anastomosis

We advise against reconstruction of the vagina with sigmoid colon after Wertheim s operation in patients who have been irradiated before the operation in aged women in cases of inflammation in the pelvis as well as in the cases where the sigmoid is short

None of the patients complained after discharge of the reconstruction of vagina there was no stress incontinence of urine with any of the patients while it is known that many patients have this difficulty after gynecological operations There could be an explanation for this in the fact that the neovagina with its mesentery gives to the bladder support similar to that given by uterus and the vagina before the operation

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Submitted for publication Nov 22 1976

Franc Novak
Department of Obstetrics and Gynecology
University of Ljubljana
Yugoslavia

Acta Obstet Gynecol Scand 57 97–103 1978

HAEMODYNAMIC EFFECTS OF OXYTOCIN (SYNTOCINON®) AND METHYL ERGOMETRINE (METHERGIN®) ON THE SYSTEMIC AND PULMONARY CIRCULATIONS OF PREGNANT ANAESTHETIZED WOMEN

N J Secher P Arnsbo and L Wallin

From the Department of Gynecology & Obstetrics the Department of Clinical Physiology and the Department of Anaesthetics Odense University Hospital Odense Denmark

ract The haemodynamic effects of oxytocin itocinon®) and methyl ergometrin (Methergin®) were ied in 9 healthy females in the first trimester of preg y The patients were anaesthetized with sodium nebumal pethidine and pancuronium bromide and ilated on a Manley respirator 10 i u oxytocin given n i v bolus brought about a fall in femoral arterial sure of 40% systemic resistance 59% and pulmonary tance 44% 30 sec after injection However the heart increased 31% and stroke volume 17% so that the iac output increased by 54% The pulmonary arterial ssure and wedge pressure were increased by 33% and respectively 150 sec after injection No changes seen in the haemodynamic parameters during infu of 80 mU oxytocin for 10 min 0 2 mg Methergin ught about an increase in the femoral arterial pressure 1% pulmonary arterial pressure 27% and wedge pres 31% with no changes in the other measured meters The use of oxytocic drugs in patients with promised circulation is discussed

e cardiovascular effect of oxytocin given in enously in the dosage required for the induction bour have been considered as minimal since the oduction of synthetic oxytocin (5 10 16 22) In trast to this several studies of pregnant women n a bolus injection of intravenous oxytocin have monstrated hypotension with a concomitant in ise in cardiac output (10 14 22) Anaesthesia s not appear to influence the circulatory effect xytocin to any great extent (2 5) Ergometrine been shown to increase the systemic and the ral venous pressures (6 9 10 23 24) but its hetic analogue methyl ergometrine (Methergin) been reported to produce much less hyperten i (8 21) The purpose of this investigation was tudy the cardiovascular effects of oxytocin itocinon) and methyl ergometrine (Methergin) he pulmonary circulation and further to compare the changes with those found in the systemic circulation

The patients were examined in the first trimester of pregnancy in order to exclude the circulatory changes caused by autotransfusion from the uterus during contraction at term

MATERIAL AND METHODS

The aim of the study and the experimental procedure was explained in detail to the patients At the same time it was stressed that there would be no therapeutic benefit from participating in the study Thereafter all the patients consented to take part The material consists of 9 healthy women age 20–37 years (mean 28) referred to the clinic for abortion in the 10th to 17th weeks of gestation The patients were anaesthetized with sodium thiomebumal pethidine and pancuronium bromide They were intubated and ventilated on a Manley respirator adjusted according to the Radford nomogram Ventilation was carried out with N_2O–O in a ratio of two to one so as to obtain as stable and reproducible circulation as possible The ECG was registered continuously and the pressure in the femoral artery measured continuously through an indwelling catheter A Swan-Ganz flow directed thermodilution catheter (93A 118 7F) was introduced into the pulmonary artery through an antecubital vein The pulmonary artery pressure the pulmonary wedge pressure and the femoral pressure were measured using pressure transducers (Elema Schonander type EMT 35) The results were registered on a recorder (Mingograph 81 Elema Schonander) The transducers used were calibrated before and after each series of measurements The output of the pulmonary and wedge pressure transducer were averaged electrically to obtain the mean pressure All the measurements were performed with the patient in the supine position and the level of the zero reference point of the pressure recordings was defined as the midaxillary line The thermistor in the Swan-Ganz catheter was connected to a cardiac output computer (Edwards 9510) the output of which was registered on a recorder (Servogor RE 570) Any abnormal curves were disregarded The

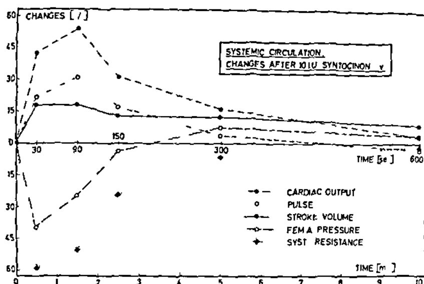


Fig 1
hemodynamic parame systemic circulation with after 10 i u oxytocin (S non®)

transthoracic electrical impedance (Z_0) which is a function of the thoracic fluid volume (17) was measured by a Minnesota impedance cardiograph model 304 A designed by Kubicek et al (15) Two aluminium strip electrodes were placed around the neck separated as widely as possible and two electrodes were placed around the abdomen The upper at the level of the xiphoid process and the other electrode 5 cm below The outer electrodes were provided with an electrical field from a constant sinusoidal current oscillator (100 kHz 4 mA)

The voltage between the two inner electrodes was measured and the impedance Z was displayed on a digital meter

PROCEDURE OF THE INVESTIGATION

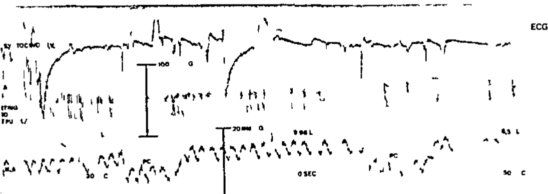
Control measurements of ECG blood pressures tho impedance and at least 5 cardiac output measure were made after completion of suction abortion

Two of the patients then received 5 i u oxyt patients received 10 i u oxytocin as a bolus through a peripheral arm vein The remaining received a constant infusion of 80 mU/min of oxy over a period of 10 min The cardiac output and thoracic impedance were measured after 30 sec and after about 90 150 300 and 600 sec respective pressure in the femoral artery was measured co

Table I *The maximal effect of oxytocin (Syntocinon®) on the haemodynamic parameters of the sy circulation*

Patient	Fem art press (mmHg)		Systemic resistance (dyn sec cm ⁻⁵)		Stroke volume (ml)		Pulse (min ⁻¹)		Cardiac output (ml
	Before	After 30 sec	Before	After 30 sec	Before	After 90 sec	Before	After 90 sec	Before
1 5 i u of Syntocinon	83	40	1 254	477	64	74	83	94	5 796
2	83	60	1 358	698	58	73	85	91	4 888
1 10 i u of Syntocinon	90	53	1 378	529	77	82	68	97	[illegible]
2	73	60	1 150	699	67	76	76	79	5 080
3	95	56	1 617	613	59	80	79	111	4 700
4	98	58	1 421	640	69	90	80	107	5 518
5	93	70	1 879	565	61	72	65	97	3 960
6	89	46	1 123	498	75	83	84	107	6 340
7	83	46	1 377	581	67	78	77	97	4 8 3
8	89	46	1 323	532	69	82	78	105	5 380
9	79	39	1 036	401	80	89	76	117	6 100
Mean	87 7	5[illegible] 7	1 367	562	69 3	81 3	75 3	98 6	[illegible]
$M \pm S D$	8 0	9 5	261	87	7 0	5 8	6 0	10 7	[illegible]

$p<0\ 001$)



2 The effect of 10 i u of oxytocin given as a bolus avenous on the pulmonary arterial pressure (*PULM A*) wedge pressure (*PCV*) and femoral arterial pressure (*FEM A*) on one subject

is was the pulmonary arterial pressure although the r was interrupted by measurements of the wedge sure After at least 10 min all the patients received an avenous bolus injection of 10 i u of oxytocin After circulation had again become stabilized all the pa s received 0 2 mg methyl ergometrine (Methergin) in enously and measurement of the haemodynamic meters was repeated for a period of about 10 min

RESULTS

e effect of 10 i u of oxytocin given as a bolus avenous injection on the haemodynamic para meters of the systemic circulation in 9 subjects are shown in Table I and Fig 1 A typical example is shown in Fig 2 The decrease in the femoral arterial pressure was most pronounced after 30-40 sec with a decrease of 40% below the control val ues the blood pressure returned to control levels after 150 sec This hypotension was followed by a concomitant increase in stroke volume as well as in heart rate The heart rate increased approximately 10 sec after the decrease in the arterial pressure and a maximal increase of 31% was obtained after about 90 sec The stroke volume increase followed

ble II *The maximal effect of oxytocin (Syntocinon®) on the haemodynamic parameters of the pulmo y circulation*

	Pulmonary resistance (dyn sec cm)		Pulm art press (mmHg)		Wedge press (mmHG)	
ent no	Before	After 30 sec	Before	After 150 sec	Before	After 150 sec
i u of Syntocinon						
	35	24	11 2	14 6	8 9	11 1
	8?	47	11 ?	13 3	6 2	7 6
i u of Syntocinon						
	7?	-	13 8	17 5	9 1	-
	90	51	13 3	13 8	7 6	8 9
	31	0	11 0	14 2	9 2	1? 3
	59	3?	9 3	12 8	5 ?	6 0
	89	18	14 4	18 0	10 0	1 8
	71	69	11 6	16 8	6 0	8 8
	65	?4	1? 1	16 0	8 ?	10 7
	54	50	9 6	14 6	6 0	8 9
	53	9	9 4	14 9	5 4	9 2
n	64 9	36 6	11 6	15 4	7 4	9 7
S D	18 5	18 1	? 0	1 8	1 8	2 ?

< 0 01

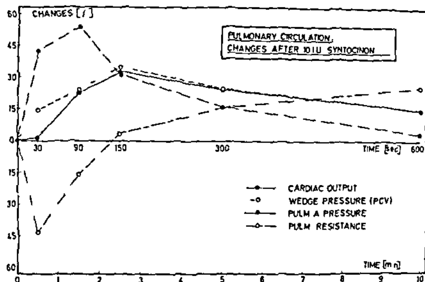


Fig 3 Percentage change in hemodynamic parameters in pulmonary circulations after 10 i u oxytocin (Syntocinon®)

the change in heart rate and maximal values of 17% of control values were recorded after 90 sec The cardiac output increased by 54% of the control value after 90 sec and a maximal decrease of 50% in peripheral resistance was observed after 30 sec The changes in systemic haemodynamics after 5 i u of oxytocin were almost as pronounced as after 10 i u (Table I) The effects of 10 i u of oxytocin given as a bolus intravenous injection on the haemodynamic parameters of the pulmonary circulation in 9 subjects are seen in Table II and Fig 3

The most striking observation was an increase in pulmonary arterial pressure this reached maximal values of 33% after 150 sec at which time the cardiac output was still elevated but the pressure in the systemic circulation was almost normal The increase in the pulmonary arterial pressure was followed by a concomitant increase of 35% in wedge pressure after 150 sec After 10 min the pulmonary and wedge pressures were still slightly but significantly elevated The pulmonary resistance decreased by a maximum of 44% after 30 sec The pulmonary resistance returned to normal after sec The changes in the pulmonary haemodynamics after 5 i u of oxytocin were almost as as those after 10 i u (Table II) Five patients received a second bolus injection of 10 i u of oxytocin and tachyphylaxis was demonstrated by a

Table III *The maximal effect of 0 2 mg methyl ergometrine (Methergin®) on the blood pressure in the systemic and pulmonary circulation*

Patient no	Fem art press (mmHg)		Pulm art press (mmHg)		Wedge press (mmHg)	
	Before	After	Before	After	Before	After
1 0 2 mg of Methergin	100	120	14 2	17 5	–	–
2	80	100	14 2	17 8	9 8	13 [illegible]
3	96	106	13 5	17 3	11 5	10 8
4	100	116	1[illegible] 5	15 0	9 5	1[illegible] 0
5	95	97	16 0	18 4	7 9	9 9
6	88	91	1[illegible] 7	15 [illegible]	6 9	10 9
7	88	94	12 5	18 4	9 8	1[illegible] 9
8	96	112	10 7	16 4	6 8	1[illegible] 0
9	83	84	11 7	13 7	8 0	9 8
Mean	91 8	102 2	13 1	16 6	8 8	11 4
M±S D	7 3	12 1	1 6	1 7	1 6	1 3

$p<0.01$ $p<0.05$

nounced change in the haemodynamics than af he first injection (heart rate 37% stroke volume cardiac output 42% systemic arterial pres 90% pulmonary arterial pressure 52% and lge pressure 64% of the maximal values after the injection)

lo changes were seen in the pulmonary nor the emic circulation after intravenous infusion of 80 of oxytocin for ten min

n increase in the pulmonary arterial and wedge sure of 27% and 31% respectively with a ht increase of 11% in the systemic blood pres were found after 0 2 mg methyl ergometrine e reached maximal values after 5 to 10 min No nges were found in cardiac output and heart

The hypertension persisted throughout the od of observation and the mean maximal pres s in the systemic and pulmonary circulation are wn in Table III

fall in thoracic impedance of 0 19 ohm was nd after 0 2 mg methyl ergometrine intravenous out no change was found after the administration oxytocin Apart from a few extrasystoles pre ably caused by manipulation of the Swan Ganz eter there were no abnormalities in the ECG ing the administration of oxytocin and methyl ometrine

DISCUSSION

r an intravenous bolus injection of oxytocin a ease in systemic arterial pressure followed by a omitant increase in cardiac output have been rted in several studies (2 4 14 22) In our y of young healthy females in the first trimes f pregnancy 10 mU of oxytocin decreased the n blood pressure by 40% with concomitant in ses in cardiac output and heart rate of 54% and respectively Nakano & Fisher (18) found in study that oxytocin increased the myocardial ractile force This effect could be caused by ocin per se or it could represent a reflex re ise due to acute vasodilatation

ur findings of an increased heart rate and stroke me which appeared later than the peripheral dilatation indicate that a reflex sympathetic ulation is the most likely explanation

fter administration of pitocin Woodbury et al found an increased pressure in the jugular vein onsignificant increase in central venous pres was found by Williams et al (23) after administration of 10 i u oxytocin post partum We have not measured the central venous pressure but the pronounced increase in cardiac output indicates an increased venous return to the heart Oxytocin has a peripheral vasodilatory effect on the vascular bed in the human extremities (11 13) The in creased venous return could not be caused by emptying of the vessels of the contracting uterus as the patient was only in the first trimester of pregnancy The increased blood return is probably caused by visceral vasoconstriction as was also demonstrated in female rats following direct microscopic exami nation (1) A concomitant factor could be an in creased sympathetic drive on the heart with the increase in cardiac output

Only a few studies have been carried out on the effect of oxytocin on the pulmonary circulation Intravenous injection of 1 i u oxytocin did not change pulmonary arterial pressure nor pulmonary vascular resistance in man (19) However it was found that continued infusion of high dosages of 10–15 i u oxytocin over a 30 min period caused a slight increase in pulmonary arterial pressure on average of 1 6 mmHg In this study (19) 9 of 15 male patients showed an increase in pulmonary arterial pressure This increase in pulmonary pressure was not associated with any change in pulmonary wedge pressure or pulmonary vascular resistance We found no change in the pulmonary arterial and wedge pressures during infusion of 80 mU of oxytocin per minute for 10 min After intravenous injec tion of 10 i u of oxytocin we have found an increase in pulmonary arterial and wedge pressures in all patients these reached maximal values of +33% and +35% after 150 sec when the systemic blood pressure was almost normal but with a cardiac output that was still elevated This increase in pulmonary pressure was preceded by a transient decrease in pulmonary vascular resistance This in crease in pulmonary and wedge pressures could be caused by the increase in cardiac output per se as seen during exercise (7)

Many investigators have reported that the circulatory effect of repeated doses of oxytocin are weaker than those of the initial doses (4 12 24) In our study the cardiovascular effect of the repeated bolus dosage of 10 i u of oxytocin was less pronounced than that following the initial dose This tachyphylaxis has been suggested as being due to a change in the response of the blood vessels to the direct actions of oxytocin (13)

The effect of oxytocin on the ECG has been studied in several investigations (12 16) Berquist (3) found not only alteration of the T wave but also occasional depression of the ST segment in post partum women Katz (12) found as we did that there were no essential ECG changes in anaesthetized patients

Oxytocin is frequently given as a bolus injection after delivery and during suction abortion although it has been stressed that oxytocin if it is to be used intravenously should be administered as a diluted intravenous infusion (10 22) Although the haemodynamic changes after an intravenous bolus injection of oxytocin were transient the haemodynamic changes could be dangerous in patients with a circulation already compromised by hypovolaemia and heart disease with a fixed cardiac output valvular stenosis or right to left shunts

It has been demonstrated that methyl ergometrine raises the central venous pressure and reduces peripheral venous compliance in healthy volunteers (6 9 23) Our results confirmed that a slight elevation in systemic blood pressure occurs after methyl ergometrine (8 21) We found in percentage a more pronounced increase in pulmonary arterial and wedge pressures after methyl ergometrine The concomitant fall in thoracic impedance of 0 19 ohm indicates an increase in thoracic fluid volume As methyl ergometrine constricts the blood vessels the fall in thoracic impedance would suggest an increase in the interstitial fluid lung volume This finding together with the reduced compliance of the venous reservoir after methyl ergometrine and its ives together with an increased blood volume after uterine contraction may be an important factor in the precipitation of pulmonary oedema and cardiac failure in patients with impaired cardiac function However the risk of post partum haemorrhage is increased if no oxytocic drug is used Therefore when treating patients with cardiac disease it is necessary to weigh the risk of pulmonary oedema and congestive heart failure following ergometrine with the possibility of a massive post partum haemorrhage if it is not administered

Prostaglandins have been used in recent years for the induction of labour and midtrimester abortion We have shown that prostaglandin $F_2\alpha$ markedly increases the pulmonary as well as the wedge pressures (20) In this study no cardiovascular changes were found during the infusion of 80 mU of oxytocin per minute Therefore oxytocin given as a dilute intravenous infusion should be the drug of choice in patients with cardiac dise

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Submitted for publication Febr 15 1977

N J Secher
Dept of Obstetrics and Gynecology YA
Rigshospitalet
Blegdamsvej 9
DK 2100 Copenhagen Denmark

Acta Obstet Gynecol Scand 57 105–109 1978

TRANSFER OF ^{51}CR PLATELETS AND ^{51}CHROMIUM IONS ACROSS THE TERM RHESUS MONKEY PLACENTA

Henk C S Wallenburg Piet H van Kessel and Anneke Brand

From the Departments of Obstetrics and Gynecology AZR Dijkzigt Erasmus Universiteit Rotterdam and Immunohematology Rijksuniversiteit Leiden The Netherlands

stract Determination of platelet life span could provide ·ful information on platelet kinetics in pregnant women e usual procedure involves injection of Cr labeled itelets into the maternal circulation Data on possible nsfer of ^{5} Cr platelets and ^{5} Cr ions across the placenta necessary to estimate the radiation dose delivered to fetus Since such data cannot be obtained in man the gnant rhesus monkey was chosen as an experimental odel In an acute animal study ^{5} Cr labeled maternal itelets with an activity of approximately 20 μCi were ected into the fetal (2 animals) or the maternal (3 ani ils) circulation and samples of fetal and maternal blood d of amniotic fluid were obtained during 2 to 3 hours In additional experiments labeled platelets were injected o the maternal circulation and samples as mentioned ove were obtained after 5 days No maternofetal or omaternal transfer of Cr tagged platelets across the mochorial placenta could be demonstrated whereas e ^{5} Chromium ions appear to cross the placenta The diation dose received by a 300 g fetus was estimated to 23 mrem based on the finding that the sum of total culating radioactivity in the fetus and radioactivity in amniotic fluid was always less than 1% of the amount radioactivity injected into the mother Accepting the alogy between the placentation of rhesus monkey and in it can be estimated that this procedure would result in radiation dose of approximately 7 mrem for a 1700 g us This would seem to be sufficiently low to allow termination of platelet survival by means of the Cr itelet technique in third trimester human pregnancy

contrast to the long standing evidence that red ood cells can cross the human placenta (8) and ecent proof of active fetomaternal transfer of mphocytes and granulocytes (14) direct evidence r passage of platelets across the hemochorial acenta is not available An indication that in man tal platelets might reach the maternal circulation n be derived from the sporadic occurrence of oimmune neonatal thrombocytopenia a condition pposed to be similar in pathogenesis to eryth oblastosis fetalis except that fetal platelets rather an red cells should provide the antigenic stimulus) The importance of the question as to whether aternal platelets can cross the placenta and reach the fetal circulation pertains to a different clinical problem In preeclampsia a significantly reduced platelet count has been reported (5) It has been suggested that this could be due to an increased consumption of platelets in maternal organs or in the placenta (7) Evidence to verify or deny this hypothesis can be produced by means of determina tion of platelet life span which involves injection of ^{51}Cr labeled autologous platelets with an activity of approximately 20 μCi into the maternal circulation (4 6) Such studies have not been performed in pregnant women because the ethics of human ex perimentation during pregnancy properly restrict the use of any research procedure in particular when it involves the use of radioisotopes until it reasonably can be expected to have no adverse effect on the fetus

Therefore the present study was designed to ob tain experimental data on the permeability or im permeability of the term hemochorial placenta to platelets and to ^{51}Chromium ions in an appropriate experimental animal model Since the experiments could only be performed with maternal platelets an additional comparative study was made on fetal and maternal platelet size

METHODS

Experiments were carried out in 7 pregnant rhesus mon keys (Macaca Mulatta) obtained from the Primate Center T N O at Rijswijk The Netherlands The duration of gestation was known on the basis of timed matings or early rectal palpation and ranged from 145 to 160 days Acute experiments were performed in 5 animals 2 animals were subjected to a study of longer duration

Surgical procedure

The 5 animals subjected to acute experiments were fasted from midnight to surgery the following morning After premedication with phencyclidine and atropine sulfate surgical anesthesia was induced with 0 2 to 0 5% fluo thane in oxygen following tracheal intubation Body

warmth was maintained with a heating pad under the animal The uterus was exposed through a midline abdominal incision and both placentas and interplacental vessels were located by transillumination (11) A chorionic interplacental vein was exposed through a small incision in the myometrium and catheterized with a silicone rubber T tube (inner diameter 0 8 mm outer diameter 1 3 mm) This technique allows sampling of fetal blood without disturbing flow in the catheterized vessel or destroying the integrity of the amniotic sac A 16-G polyvinyl catheter advanced into the inferior vena cava from a saphenous vein provided access to the maternal circulation During the experiments amniotic fluid was obtained by repeat puncture through the lower uterine segment After the experiments the fetus was either left in the uterus to be vaginally delivered or a Cesarean section was performed All mothers survived of the fetuses three survived and two died shortly after the experiments were finished

Preparation administration and sampling of ^{51}Cr platelets

Maternal monkey platelets were labeled with ^{51}Cr according to the technique described for human platelets by Aster & Jandl (4) and de Koning (6) which will be only briefly summarized here

Approximately 100 ml of venous ACD blood were drawn by femoral venipuncture from each animal prior to surgery and a platelet concentrate was prepared by differential centrifugation with excess ACD added before the second centrifugation step The red cells were retransfused into the mother The platelet concentrate was incubated with 150 μCi of sodium chromate (^{51}Cr) for 30 min at 22°C washed with platelet poor plasma and resuspended in fresh platelet poor plasma Thus ^{51}Cr labeled platelets with an activity of approximately 70 μCi in a volume of 4–5 ml of plasma were obtained In the acute preparations the ^{51}Cr platelets were injected into the fetal interplacental vein in 2 monkeys and into the maternal inferior vena cava in 3 animals Following injection of the labeled platelets samples of 5 ml of maternal and of 1 ml of fetal [illegible]DTA blood and of amniotic fluid were simultaneously [illegible]d at regular predetermined intervals over a 2 to 3 [illegible] period of time In 2 animals autologous ^{51}Cr platelets [illegible]re injected into the maternal circulation under brief [illegible]ncyclidine analgesia and gestation was allowed to continue for 5 days After that period of time a cesarean section was performed and simultaneous samples of 5 ml of maternal and of 1 ml of fetal blood and of amniotic fluid were obtained

Radioactivity in all samples was simultaneously assayed in a well type gamma scintillation counter with corrections made for background radiation The concentration of radioactivity in maternal blood was determined separately in the total cell fraction in the erythrocytes and in the platelet poor plasma Since virtually no activity above background level was found in the erythrocytes the amount of platelet bound ^{51}Cr radioactivity could be calculated by correcting the amount of radioactivity in the total cell fraction for the activity in the 70% of the total platelet poor plasma volume which was estimated to remain adherent A similar procedure was followed for the assay of platelet bound radioactivity in the fetal samples except that red cell radioactivity could not be [illegible] determined due to the small sample volume [illegible] maternal blood volume and of amniotic fluid volume [illegible] based upon maternal weight fetoplacental blood volume was estimated from fetal weight On the basis of [illegible] estimates radioactivity found in maternal and fetal [illegible] and in amniotic fluid was calculated as a percentage of injected dose

Measurement of platelet volumes

Maternal and fetal platelet volumes were [illegible] three mother–fetus pairs and compared with [illegible] obtained in three non pregnant female monkeys [illegible]tial counting of platelets in samples of platelet rich pl[illegible] prepared from blood collected in 3 8% sodium citrate [illegible] performed with a Coulter FN (70 µ tube) coupled [illegible] Channelyser C 1000 Thus curves were obtained [illegible]sing the relative frequency of platelet volumes [illegible] range from 1 75 to 1 79 $\mu 3$

RESULTS

The concentration of radioactivity in blood and plasma is presented as the ratio of radioac[illegible] each sample to the total amount injected (Tabl[illegible] With these data the approximate percentage of [illegible]jected radioactivity found in each of the va[illegible] compartments was computed

Injection of ^{51}Cr platelets into the maternal circulation

After 8 minutes between 70 and approximately [illegible] of the total amount of radioactivity injected [illegible]peared to be present in the circulating blood after [illegible] hours total circulatory activity was still between [illegible] and 90%

In two monkeys 30 and 20% respectively of [illegible] total amount of radioactivity administered was [illegible] present in maternal blood after 5 days During [illegible] to three hours after injection of the labeled pl[illegible] into the maternal vena cava approximately [illegible] of the total radioactivity in maternal blood [illegible] found in the platelet poor plasma fraction [illegible] days radioactivity in plasma was 5 and 7% [illegible]tively of the total blood radioactivity at that [illegible] Cell bound radioactivity could not be demonstra[illegible] in any of the fetal samples The concentration of radioactivity in fetal plasma varied between [illegible] 10% of the concentration in maternal plasma du[illegible] the period of two to three hours following [illegible] of the isotope into the maternal circulation [illegible] in monkey no 2323 where it rose to 22% [illegible] hours Total circulating activity in the fetus [illegible] computed to vary between 0 003% of the total [illegible]

ble 1 *Ratio of c p m per ml/c p m in total dose of ^{51}Cr administered $\times 10^{-4}$ after administration of* *μCi of ^{51}Cr platelets*

	Maternal weight (kg)	Fetal weight (g)	Ratio in maternal blood/Ratio in maternal plasma						Ratio in fetal plasma					
			8	30	60	120	180 min	5 days	8	30	60	120	180 min	5 days
r platelets injected into maternal circulation														
51	8 8	385	16 04/0.57	14 75/0 33	–	14 66/0 .6	14 34/0 0	–	0 02	0 01	0 0?	0 02	0 01	–
	8 5	500	17 97/0 33	14 25/0 24	14 97/0 8	15.58/0.31	–	–	0 01	0 01	0 02	0 01	–	–
.3	5 5	400	?9 90/0 25	29 30/0 21	29 15/0 34	27 35/0 19	–	–	0 02	0 02	0 03	0 04	–	–
41	7 1	440	–	?0 37/0 55	–	–	–	7 09/0 5.	–	–	–	–	–	0 13
53	7 4	510	19 56/0 51	19 60/0 21	–	–	–	4 70/0 24	–	–	–	–	–	0 03
			Ratio in maternal plasma						Ratio in fetal blood/Ratio in fetal plasma					
ected into fetal circulation														
)	5 8	340	0 06	0 0?	0 06	0 05	0 04	–	3?0 1	–	–	–	–	
11	6 7	480	0 08	0 08	0 08	0 09	0 04	–	31? 91/16 24	233 54/6 70	?44 9?/5 29	?41 ?1/5 83	?21 50/5 18	

radioactivity administered to the mother at 8 min d up to 0 03% at 5 days after injection

Radioactivity could not be detected in amniotic id samples taken 8 min after injection In two als a small amount of radioactivity was demon d in amniotic fluid samples obtained from 30 n to 3 hours after injection ratios varied from 01 to 0 003 One amniotic fluid sample drawn 5 ys after injection had a ratio of 0 02 which with amniotic fluid volume of 70 ml represents a total ount of radioactivity in the amniotic fluid of this imal of 0 01% of the total dose administered

iection of ^{51}Cr platelets into e fetal circulation

the two experiments performed between 65 and % of the total dose of radioactivity administered as recovered in the circulating fetal blood be 2 and 5% of the activity in fetal blood was esent in the platelet poor plasma fraction No ll bound activity was detected in maternal blood adioactivity was present in the amniotic fluid 8 in after injection in one animal and after 30 min in th monkeys the ratios varied between 0 11 and 03 over a sampling period of 3 hours

The curves of distribution of platelets volumes in pregnant and in non-pregnant animals were similar All fetal curves showed a small shift to the left as compared with the maternal distribution curves (Fig 1) The average mode of fetal platelet volume was 3 5 μ^3 and that of the mother 4 2 μ^3

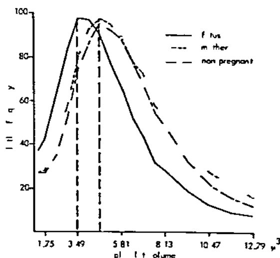


Fig 1 Distribution of platelet volumes in a rhesus monkey mother–fetus pair and in a nonpregnant animal

DISCUSSION

Fetomaternal transfer of platelets cannot be experimentally studied in man because the fetal circulation is not accessible unless under the most exceptional circumstances Also techniques for studying fetomaternal transfer of white cells using the fluorescent Y chromatin as a marker cannot be applied relative to platelets (14) An experimental study on maternofetal transfer in man could technically be done by injecting autologous ^{51}Cr platelets into the maternal circulation a few days before or during delivery and counting a cord blood sample after delivery of the baby Since no data were available on the possible extent of transplacental passage of ^{51}Cr platelets or on the behavior of free ^{51}*chromium* *this approach was considered unacceptable* because of the possible radiation hazard to the fetus For these reasons the rhesus monkey was chosen as an *experimental model* *The close similarity* between fetal and maternal placental circulation vasculature and villous morphology in this animal and man has been demonstrated (10) Assuming that labeled and nonlabeled platelets are indistinguishable no maternal platelets appear to cross the hemochorial placenta in either direction under the conditions of the present experimental design It appeared technically impossible to prepare a labeled fetal platelet suspension due to the small fetal blood volume Though the results of measurement of platelet volumes show that the fetus has a somewhat larger proportion of smaller platelets in comparison with the mother the difference is too small to expect any influence on placen transfer

To explain the occurrence of isoimmune neonatal thrombocytopenia which has an incidence of approximately 1 or 2 per 10 000 births (12) it could be hypothesized that under sporadic and unknown circumstances fetal platelets are actively transferred to the maternal circulation However a more likely explanation is that fetal platelets constitute *part of small amounts of fetal blood that have been* demonstrated to leak through minute breaks of villous vessels (13) Since this appears to occur frequently and since maternal fetal incompatibility of platelet antigens is not unusual (12) antigenicity should be low

^{51}Chromium appears to cross the hemomonochorial placenta whereas no significant amounts are said to be transferred across the hemotrichorial placenta of the rat (3) The radiation dose received by the monkey fetus when 20 μCi of ^{51}platelets are *administered to the mother* can be estimated on the basis of the finding that no platelet-bound radioactivity passes across the placenta and that the sum of the total circulating radioactivity in the fetus and the radioactivity in the amniotic fluid will be less than 1% of the amount of radioactivity injected into the mother The radiation dose to the fetus will be virtually equal to the sum of the average radiation dose received from the radionuclides in maternal tissues (compartment A) and the radiation received from free ^{51}Cr ions transferred to the fetal tissues and the amniotic fluid (compartment B)

The biological half life (T_{biol}) of ^{51}Cr in compartment A can be estimated as being 30 days on the *basis of known data on* ^{51}Cr labeled red cell survival with 50% spleen uptake (9) this is probably a slight overestimate The physical half life (T_{phys}) of ^{51}Cr is *27 8 days Therefore effective* half life (T_{eff}) can be calculated to be equal to 15 days Because the rate with which the fetus eliminates the ^{51}Cr radioactivity is unknown and probably low we shall assume T_{biol} in compartment B to be infinite it then follows that T_{eff} in compartment B is equal to 28 days

Compartment A contains approximately 99% of the total radioactivity administered thus (1) 15×0 99×1 44=21 4 μCi days for a dose of 1 μCi The factor 1 44 represents the integral with which the initial decay rate has to be multiplied to give total decay

Compartment B contains approximately 1% of the total radioactivity thus (2) 28×0 01×1 44 0 4 μCi days

With these data the dose of radioactivity received in rem per μCi day can be derived by comparison and interpolation from existing tables (1) The fetal dose received from compartment A will be equal to (3) 1 2×10 $^{-5}$×21 4=0 25 m rem/μCi

The radiation dose received by the fetus from compartment B depends on fetal mass and dimensions The dose for a 300 Gm fetus is 2 2×10 $^{-3}$ rem/μCi day resulting in (4) 2 2×10 $^{-3}$×0 40 0 9 m rem/μCi The radiation dose for a 1 700 g fetus is 2 9×10 $^{-4}$ rem/μCi day and therefore this fetus will receive (5) 2 9×10 $^{-4}$×0 40=0 12 *m rem/μCi* from compartment B

After administration of 20 μCi of ^{51}*Cr* labeled *platelets to the mother* the radiation dose to a 300 Gm rhesus monkey fetus can be computed by combining the dose from compartment A (3) and compartment B (4) thus (6)20×(0 25+0 9)=23 m rem

f we extrapolate our monkey data to a human us with a weight of 1700 g the dose received from npartment A (3) would not change but the con ution from compartment B would be only 0 12 m /μCi (5) and the total dose could be estimated as 70×(0 25+0 12)=7 4 m rem

For fetuses weighing more than 1700 g the total iation dose received would be lower because of ir greater mass and dimensions (1) In man a fetal ght of 1700 g is normally found at approximately weeks of pregnancy If we accept the analogy ween placentation in man and rhesus monkey radiation hazard to the human fetus due to ministration of 20 μCi of ^{51}Cr labeled platelets to mother appears to be sufficiently small to allow ermination of platelet life span with ^{51}Cr au ogous platelets in the third trimester of preg ncy

ACKNOWLEDGEMENTS

e authors wish to thank Dr L M van Putten for his p in estimating the fetal radiation dose and Mrs P tmans for her valuable technical assistance

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Submitted for publication July 4 1977

Henk C S Wallenburg
Dept of Obstetrics and Gynecology
AZR Dijkzigt
Dr Molewaterplein 40
Rotterdam 3001
The Netherlands

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Acta Obstet Gynecol Scand 57 111–112 1978

IMPROVED METHOD FOR HYSTEROGRAPHIC EVALUATION OF UTERINE SCAR

Yoram Beyth

From the Department of Obstetrics and Gynecology Hadassah University Hospital Jerusalem Israel

well healed uterine scar is known to be one of the for successful vaginal delivery in pre Cesarean section patients An uneventful st operative course used to be accepted as a arantee of satisfactory scar repair while symp of endometritis were regarded as suggestive of red healing (1 4)

terography performed after Cesarean sec was introduced for evaluation of the scar in r to improve prediction of the prognosis of a sequent vaginal delivery (1–6) Hysterography lineates the configuration of the uterine cavity ding the anterior aspect of the lower uterine ment (1–6) Several irregularities have been de on post Cesarean hysterographies which re interpreted as due to scarring and as having or prognostic significance for vaginal delivery In s communication an improved diagnostic method is described which defines more exactly the relationship of uterine cavity irregularities to the scar

METHOD

At the time of the Cesarean section after closure of the first layer of the uterine incision three Tantalum clips (Hemoclip Edward Weck & Co New York) 5 mm in length are clipped into the myometrium one at each end of the incision and the third at an intermediate site The second layer of the uterine incision is then closed leaving the clips embedded in the myometrium Six months after surgery hysterography is performed with anteroposterior (Fig 1) and lateral views

DISCUSSION

Hysterography is an accepted method for evaluation of the uterine scar after Cesarean section and

Fig 1 Anteroposterior view Hysterogram performed six months after delivery by Cesarean section Three Tantalum clips are embedded in the myometrium at the site of a lower segment transverse scar one clip at each end and the third at an intermediate site

contributes to decision making in the management of a subsequent delivery (1–6) Defects of uterine cavity configuration have been detected in up to 100% of instances (4) but their significance is controversial The defects have been graded into four classes according to their depth (2 5) and it has been assumed that the depth correlates inversely to the thickness of the uterine wall at the scar

Hysterography performed after insertion of clips as described above provides additional information first as a marker the clips permit precise localization of the scar and its relationship to hysterographic defects Second knowing the length of the clips it may be possible to estimate the minimal thickness of the uterine wall in the region of the defect The thickness of the myometrium may be more significant prognostically than the depth of the hysterographic defect Finally the distance between the outermost clips indicates scar length An incision 10–12 cm long at surgery shrinks to 2–3 cm at hysterography six months postoperatively A correlation between the outcome of subsequent pregnancies and scar length may provide information which will give hysterography greater predictive value in the future

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Submitted for publication February 15 1977

Y Beyth
Department of Obstetrics and Gynecology
Hadassah University Hospital
P O Box 499
Jerusalem
Israel

Acta Obstet Gynecol Scand 57 113–119 1978

PLASMA LEVELS OF NON CONJUGATED OESTRONE IN HIGH RISK PREGNANCIES

O Axelsson B S Lindberg B A Nilsson and E D B Johansson

From the Department of Obstetrics and Gynaecology University of Uppsala Uppsala Sweden

tract Plasma levels of non conjugated oestrone[1] were sured with a radio immunological method in women i complicated pregnancies during the last trimester omparison was performed between values of normal nancies from a previous report (3) and those of patho-al pregnancies Women with severe pre eclampsia e found to have low values and to some extent the rone level could predict fetal outcome In pregnant ents with long standing diabetes mellitus the plasma ls of oestrone seemed to be higher than those of omplicated pregnancy In women with pregnancies iplicated by Rh isoimmunization oestrone plasma ls were similar to those found in normal pregnancies

asurements of urinary oestrogens have long n used as an aid in the care of high risk obstetric ients (9 18) To collect a 24-hour urine sample nconvenient and it is easy to loose urine voided ing defecation Drugs administered to the mother sometimes interfere with the analyses (1 2 4) changes in renal clearance of oestrogens may ur during abnormal pregnancies (5) Because of plasma oestrogen assays would be more suit to use in obstetrics as indices of fetal wellbe In recent years many investigations of plasma trogens and high risk pregnancies have been lished However only few of them have dealt i oestrone (8 17 19 20 22 25) We have re ted (3) of a rapid and reliable radio-immuno ay for plasma oestrone and its application to nor pregnancy In the present investigation this hod was used to measure plasma levels of non jugated oestrone in women with high risk preg cies

MATERIAL AND METHODS

iects

majority of the patients were treated and delivered at University Hospital of Uppsala A few patients were dled in large departments of Obstetrics and Gynaeco- at other hospitals Ante-cubital vein blood was with n into heparinized glass tubes Plasma was separated by centrifugation and stored at −20°C until assayed The plasma specimens were obtained during different weeks of pregnancy Most patients were sampled at least twice at varying intervals The diagnosis and classification of pre eclampsia were made according to the recommendations of the U S Committee on Maternal Welfare issued in 1952 (10) All mothers with Rh isoimmunization had anti D antibodies which were demonstrated by the indirect Coombs technique The infants born alive were Rh positive and had a positive direct Coombs test The still born infants showed signs of severe haemolytic disease at autopsy

The White classification was used for the patients with diabetes mellitus (16)

Assay method

A radioimmunoassay was used to estimate oestrone in plasma The per cent crossreaction of the antiserum was calculated to 3 3 for oestradiol 17β and 1 4 for oestriol (3)

Statistical methods

Mean plasma levels of oestrone in the different patho logical groups were statistically tested against the means in the corresponding gestational weeks of normal preg nancy (3) In order to test the hypothesis of no difference between groups analyses of variance were performed If this hypothesis was rejected 95% simultaneous con fidence limits for differences between group means were calculated according to the method of Scheffe (21)

RESULTS

Pre eclampsia

The plasma levels of non conjugated oestrone in patients with mild pre eclampsia are shown in Table I and Fig 1 During the last month of pregnancy the mean values and most of the individual values were spread evenly within the normal range In pa tients with severe pre eclampsia (Table I Fig 2) the mean plasma levels of oestrone were generally

[1] The following abbreviations and trivial names are used oestrone=3 hydroxy 1 3 5(10)-oestratriene 17-one oes tradiol 17β=1 3 5(10)-oestratriene 3 17β-diol oestriol= 1 3 5(10)-oestratriene 3 16α 17β triol progesterone=4-pregnene 3 20-dione

Table I *Plasma levels in ng/ml of unconjugated oestrone in pregnant women with pre eclampsia*
The figures in parenthesis are the corresponding means from normal pregnancy (3) *n* = number of patients

	Mild (*n*=86)			Severe (*n*=20)		
Weeks of pregnancy	No of samples	Mean	Range	No of samples	Mean	Range
30	2	5 3 (6 8)	2 8– 8 6	4	5 0 (6 8)	1 4– 7 0
31	1	4 2		2	3 1	[illegible]0– 4[illegible]
32	1	4 8 (6 3)		3	3 9 (6 3)	1 4– 5 8
33	2	3 3	3 2–3 4	3	6 4	[illegible]8– 9[illegible]
34	3	7 5 (6 2)	3 2–12 8	3	3 7 (6 2)	2 0– 6 2
35	6	6 0	1 4–11 8	4	4 3	[illegible]– 9 0
36	9	7 6 (6 6)	1 6–14 5	7	5 2 (6 6)	1 2–14 0
37	20	9 4 (7 7)	2 6–28 5	4	8 6 (7 7)	2 2–15 3
38	29	10 4 (9 4)	1 6–34 5	4	6 9 (9 4)	6 0– 8 6
39	34	9 6 (8 4)	0 8–20 3	6	8 5 (8 4)	3 8–1[illegible] 6
40	30	8 9 (8 6)	1 0–23 5	1	21 0 (8 6)	
41	16	12 1 (11 1)	2 6–32 0			
42	4	8 8 (8 5)	5 0–13 0			

lower than those of the normal series Most individual values were found in the lower part of the normal range No recordings exceeded the upper normal limit but a few ones fell below the lower limit

The differences in oestrone plasma concentrations between pre eclamptic and healthy women were not statistically significant Two infants of mothers with pre eclampsia were stillborn In one of these women the plasma levels of oestrone were at the lower normal limit Prior to the death of the fetus the values fell below this limit (Fig 2) In the other case the oestrone plasma concentrations were within the normal range and the death of the i could not be predicted by decreasing oestrone p ma levels This infant however showed mu malformations which was considered as the ca of death

The outcome of pregnancy in the seven p eclamptic patients with at least one plasma oest value of 2 5 ng/ml or less after the 35th wee gestation is compared to the outcome of those higher values in Table II This was performed attempt to define a fetal danger zone" v of 2 5 ng/ml or less were associated with still low Apgar scores or low birth weights in a

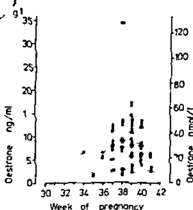


Fig 1 Plasma levels of unconjugated oestrone in patients with mild pre-eclampsia In this and the following figures the mean and spread (±2 S D) in healthy pregnant women are indicated as background (3)

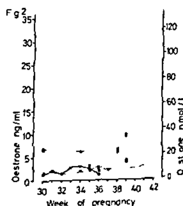


Fig 2 Plasma levels of unconjugated oestrone in with severe pre-eclampsia The line connects valu one case of intrauterine death

ɔle II *The outcome of pregnancy in pre eclamptic patients in relation to the plasma levels of oestrone r the 35th week of pregnancy*

ma level estrone	Patient group	Pa tients	Still born infants	Infants with an Apgar score of 6 or less at 1 min	Birth weight of infants: Between 1 and 2 S D below normal	Birth weight of infants: More than 2 S D be low normal	Uneventful delivery none small for date infants
ng/ml or s in at st one nple	Mild	4	0	0	2	1	1
	Severe	3	1	1	0	2	1
amples re than ng/ml	Mild	76	1[b]	6[b]	14	6[b]	54
	Severe	12	0	4	5	5	2

cording to Engstrom & Sterky (7)
ase of severe malformation
ase of a complicated breech presentation

s When all recorded values were above 2 5 ng/ the corresponding figure was 36% In the ref nce group of women with uncomplicated preg cies less than 5% occasionally showed oestrone ma values of 2 5 ng/ml or less after the 35th k of pregnancy

betes mellitus

r plasma levels of oestrone in pregnant women 1 diabetes mellitus are shown in Table III and 3 and 4 In patients with a short duration of r diabetes (White groups B and C) the mean ls were fairly constant from the 30th to the 40th k of pregnancy and tended to be higher than e of normal pregnancy The individual values were predominantly within the normal limits al though a few women had remarkably high values Two cases of intrauterine fetal death occurred in this group These patients had oestrone plasma levels in the upper normal range A moderate in crease in plasma oestrone was noticed prior to the fetal death (Fig 3) In women with longstanding diabetes mellitus (White groups D F and R) the mean levels were even higher No rise in the mean plasma concentration of oestrone with advancing pregnancy was observed during the last trimester The majority of the values were found in the upper normal range Some patients showed notably high values The differences in plasma oestrone levels between diabetic and healthy women were not sta tistically significant

le III *Plasma levels in ng/ml of unconjugated oestrone in pregnant women with diabetes mellitus* figures in parenthesis are the corresponding means from normal pregnancy (3) n=number of patients

ks of nancy	White groups B and C (n=39): No of samples	Mean	Range	White groups D F and R (n=8): No of samples	Mean	Range
	6	10 3 (6 8)	5 4–16 8	3	16 0 (6 8)	1 7–35 0
	3	12 ?	2 6–?4 8	3	15 3	1 6–31 6
	5	7 5 (6 3)	3 8–11 4	4	12 3 (6 3)	6 2– 4 5
	6	9 8	1 8–16 5	3	13 5	7 4–24 4
	9	9 9 (6 ?)	3 2–17 8	6	11 6 (6 2)	4 4–23 5
	14	9 1	2 0–32 0	5	17 6	6 8–31 3
	?2	10 5 (6 6)	1 6–?4 0	4	15 9 (6 6)	8 8–?8 8
	19	9 0 (7 7)	1 4–?3 3	4	8 7 (7 7)	8 0–10 8
	15	7 0 (9 4)	1 8–1? 8	1	18 ? (9 4)	–
r	9	9 0 (8 4)	3 2–18 5			
	3	11 4 (8 6)	3 2–23 3			

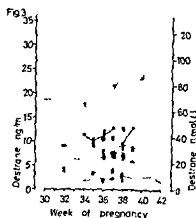


Fig 3 Plasma levels of unconjugated oestrone in patients with diabetes mellitus (White groups B and C) The lines connect values from two cases of intrauterine fetal death

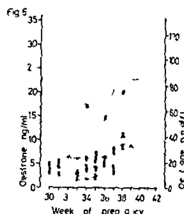


Fig 5 Plasma levels of unconjugated oestrone in p... with mild to moderate Rh immunization (cord ... than 80 g/l)

Rh immunization

The results of the plasma oestrone estimations in patients with Rh immunization are shown in Table IV and Figs 5 and 6 In mothers of infants with mild to moderate hemolytic disease the mean levels of plasma oestrone were mostly lower than those of the normal series The differences were not statistically significant Most values fell within the normal range The oestrone plasma levels in women with severe Rh immunization differed only slightly from those of the reference group Three patients were sampled 2–4 days after fetal demise At that time the oestrone plasma values were still within the normal range and in one case no decrease could be observed (Fig 6)

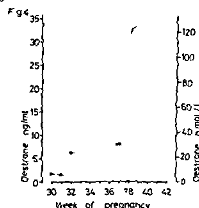


Fig 4 Plasma levels of unconjugated oestrone in patients with diabetes mellitus (White groups D F and R)

DISCUSSION

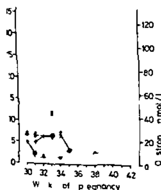
Previous investigations on plasma or blood le... oestrone in women with pre eclampsia ha... vealed that low or subnormal values are com... found especially when pre eclampsia is asso... with stillbirth neonatal asphyxia or low b... weight (8 19) Kubli & Keller (1?) presented s... results In their report however oes... oestradiol 17β were not assayed separately ... above mentioned reports total (unconjugated... jugated) oestrone in plasma or blood were ... ured The low oestrone levels are supposed ... flect an impaired placental function Altho... present study gives plasma levels of unconj... oestrone the results are in good agreement ... previous works in that low or subnormal v... are common in patients with severe pre-ecla...

An attempt to establish a fetal da ger ... showed that intrauterine death neonatal a... or low birth weight frequently occurred at oe... levels of 2 5 ng/ml or less after the 35th we... pregnancy One case of fetal death occurred ... higher oestrone plasma level this f tus ha... had severe malformations Signs of fetal d... low Apgar scores or low birth weight were ... served in about 35% of the patients even th... all recorded oestrone plasma values ex... ng/ml Loriaux et al (14) suggested that mea... ment of any plasma oestrogen could be used ... sess feto-placental function Other author... claimed that measurement of oestriol gives th... adequate information about the fetal state (... 13) Dumont et al (6) have stated that est...

le IV *Plasma levels in ng/ml of unconjugated oestrone in pregnant women with Rh isoimmunization*
figures in parenthesis are the corresponding means from normal pregnancy (3) n = number of patients

ks of nancy	Cord blood haemoglobin more than 80 g/l (n = 6?)			Cord blood haemoglobin 80 g/l or less (n = 15)		
	No of samples	Mean	Range	No of samples	Mean	Range
	6	4 3 (6 8)	2 8– 6 8	4	6 4 (6 8)	5 0– 7 ?
	9	5 0	2 6– 9 0	4	5 2	2 4– 7 0
	9	4 0 (6 3)	1 4– 7 4	8	6.3 (6 3)	1 6–11 2
	13	5 0	1 6–13 5	6	7 3	1 6–12 0
	14	8 9 (6 2)	1 8–25 5	8	7 2 (6 ?)	1 4–13 0
	17	5 4	1 8–10 8	4	9 5	3 ?–16 3
	16	8 6 (6 6)	3 6–21 8	4	9 6 (6 6)	4 6–16 0
	1?	7 ? (7 7)	3 0–15 3			
	16	1? 4 (9 4)	3 4–?9 8	1	3 0 (9 4)	
	5	6 4 (8 4)	3 0–10 0			
	2	6 4 (8 6)	4 8– 8 0			

unconjugated oestrone in plasma is less suitable use in this connection because of the large ad of the normal values Mathur et al (17) have attention to the fact that plasma from pre ımptic patients can convert oestradiol 17β to They suggest that the use of oestradiol in the management of high risk pregnancies be combined with measurement of oestrone present study shows that plasma values of un jugated oestrone may be used as an index of l well being in patients with pre eclampsia al ıgh false positive as well as false negative indi ons are rather common



6 Plasma levels of unconjugated oestrone in patients severe Rh immunization (cord Hb 80 g/l or less) and in patients with intrauterine fetal death due to re hemolytic disease = + The values denoted ⊕ ong from samples taken ?–4 days after the death of the

Divergent results have been published about plasma levels and urinary excretion of oestrogens in diabetic pregnancy In a report from 1970 Lyngbye (15) presented a review on the subject Roy & Kerr (20) found low blood levels of total oestrone in pregnant women with diabetes mellitus Most values however were within the normal range The authors suggested that the observed low levels seemed to be more related to associated conditions such as pre eclampsia rather than primarily to the diabetes In the present study a few diabetic women had their pregnancy complicated with pre eclampsia With one exception the oestrone plasma levels in these patients were low or subnormal In one woman high values were recorded This patient however was also suffering from a renal disease Wodrig & Goretzlehner (25) presented significantly lowered values of unconjugated oestrone in blood in patients with diabetes mellitus Our results on the other hand are in agreement with those of Svendsen & Sorensen (22) who found high plasma levels of unconjugated oestrone in two pregnant women with diabetes They suggest that these high oestrone values might reflect the large placentas found in diabetic patients

The conflicting findings on oestrone levels in plasma of diabetic women during pregnancy may be due to the fact that diabetes is a heterogenous disease in regard to duration severity and principles of treatment Estimation of the plasma levels of unconjugated oestrone seems to be of no use in predicting the outcome of diabetic pregnancies

Previous investigations on plasma oestrone in

women with Rh immunization are few Fischer Rasmussen (8) who measured total oestrone in plasma found values well within the normal range in two women with Rh immunization One of these women delivered a healthy infant In the other case an intrauterine death occurred These findings are in accordance with the results of the present report which indicate that no correlation exists between the haemolytic process in the fetus and the plasma levels of oestrone in the pregnant woman Tulchinsky & Korenman (24) observed high and rising plasma values of oestradiol 17β in two cases of intrauterine fetal death A similar trend was not observed in the three cases of intrauterine fetal death in the present study Oestrone plasma values recorded after fetal death were within the normal range (Fig 6) The same observation has been described for oestradiol 17β (24) Persisting normal values of these hormones despite clear evidence of fetal death seem to be connected with the hypertrophied placenta found in these patients There are no indications that measurement of plasma oestrone itself could be of any use in evaluating fetal prognosis in patients with Rh immunization As pointed out by Lindberg et al (13) and Tulchinsky et al (23) measurement of the oestradiol 17β/oestriol ratio in plasma possibly in combination with the progesterone/oestriol ratio is helpful for predicting fetal well being in Rh haemolytic disease

CONCLUSION

The levels of nonconjugated oestrone in maternal ısma will to some extent reflect the fetal state in s with pre-eclampsia In pregnant women ith diabetes mellitus or Rh immunization the oestrone plasma levels could not be used to predict fetal outcome

ACKNOWLEDGEMENT

This study was supported by the Ford Foundation the Swedish Medical Research Council (Grant No 3495) the Expressen Fund for Prenatal Research and the Allmänna Barnbördshusets Mödrahemsdelegation

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Submitted for publication Sept 9 1976

O Axelsson
Department of Obstetrics and Gynecology
University Hospital
750 14 Uppsala
Sweden

Acta Obstet Gynecol Scand 57 121–124 1978

PLASMA STEROIDS IN THE FOETAL AND MATERNAL CIRCULATION AT NORMAL DELIVERY AND ELECTIVE CAESAREAN SECTION

P Coats E Florensa E Youssefnejadian and I Craft

From the Institute of Obstetrics and Gynaecology Queen Charlotte s Hospital London England

stract Maternal and foetal plasma collected at normal ivery and at elective caesarean section was assayed for steroid levels Foetal cord plasma concentrations progesterone 17 hydroxyprogesterone oestrone and triol were higher than maternal values at normal deliv whereas oestradiol levels were lower Oestrone con itrations were higher than oestradiol in the foetal circu on at normal delivery and oestrone values were higher owing normal delivery than at elective caesarean sec 1

term approaches and labour progresses a chang endocrine environment occurs within the to-placental unit The nature of this change has n variously investigated in the human situation no agreement has been reached (8 9 10) Ani l studies indicate a striking rise in 17 β oestradiol ducing a contrary action on the myometrium to gesterone (?) and in premature human labour vated levels of oestradiol have been reported)

The purpose of this study reported here was compare oestrone oestradiol oestriol pro- terone and 17 hydroxyprogesterone concentra ıs in the foetal and maternal circulations at nor l delivery and at elective caesarean section to luate their inter relationships and their associa ı with parturition

MATERIALS AND METHODS

0 ml of heparinised blood was collected in each in ice and the plasma separated and stored at −20°C prior analysis Radioimmunoassay of oestrone oestradiol triol progesterone and 17 hydroxyprogesterone was formed using radioimmunoassay techniques previously orted (5 13 14 15)

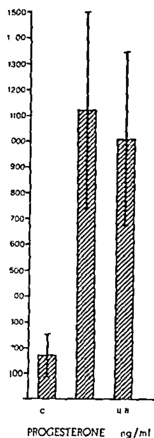
RESULTS

e mean and standard deviation of individual roid hormones in the maternal and foetal plasma following normal delivery and expressed in ng/ml are shown in Figs 1 and 2 The concentrations of oestrone oestriol progesterone and 17 hydroxyprogesterone were significantly greater in umbilical venous plasma compared with maternal peripheral venous blood whereas oestradiol levels were significantly lower (Table I) Oestrone con centrations were significantly greater in the umbili cal vein compared to the umbilical artery (37 9±9 8 compared with 28 5±10 6 $t=5\ 52$ $p=<0\ 01$) but differences in the concentrations of the other steroids in the foetal umbilical vessels were not significant (Fig 2)

The results from blood taken at elective cae sarean section in three subjects corrected to the nearest whole number are shown in Table II Pro- gesterone and oestriol levels were markedly higher in the foetal than in the maternal circulation Oestrone levels were also raised in the foetal samples but the range detected (24 6–29 8) was considerably lower than the mean value found following normal deliv ery (37 9) Oestradiol levels were lower in the foetal than the maternal circulation at normal delivery

DISCUSSION

Changes in oestrogen metabolism occur in the foetoplacental unit in late human pregnancy The finding of higher oestrone concentrations in the foetal circulation following normal delivery than at caesarean section confirms the results of Patten et al (8) Oestrone is in higher concentration in the foetal than in the maternal circulation and is higher in the umbilical vein compared to the umbilical artery supporting the concept that changes in oestrone production occur in the placenta in associ ation with spontaneous labour since there were no such differences at elective caesarean section The biologically more potent oestradiol was in lower



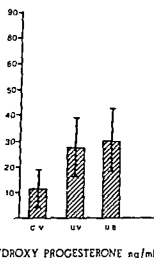


Fig 1 Plasma steroids in the foetal and maternal circulation normal delivery—progesterone

concentration in the umbilical vein compared to the artery and higher in the maternal venous plasma at normal delivery which may be evidence for a mechanism metabolising oestradiol in the placenta which protects the foetus

Prostaglandin concentrations are also increased in the foetal circulation in late human pregnancy (4) but the significance of the finding and its possible inter relationship with the changing steroid environment at the onset of spontaneous labour is uncertain Progesterone and 17α hydroxyprogesterone are found in higher concentrations in the foetal compared to the maternal circulation (6) both before and following the onset of parturition and the finding that foetal progesterone values are higher rather than lower following normal delivery than in late pregnancy suggests that this steroid hormone is not so involved in the initiation of parturition in the human as in other animal species

Oestrogen production in the foeto-placental unit is regulated by foetal adrenal function (1) and umbilical arterial and venous levels of ACTH are greater in spontaneous than in induced labour probably indicating a pituitary adrenal oestrogen metabolism link It may be that the development of progressive uterine contractions indicative of

Table I *Steroid concentrations in maternal cubital vein and umbilical vein plasma at normal d*
(n=19)
Mean ±S D

	Progesterone	17 hydroxy progesterone	Oestrone	Oestradiol	Oestriol
Cubital vein	163± 81	11 1± 7 1	10 9±5 3	29 8±15 3	90 6± 6
Umbilical vein	1 119±379	27 6±10 0	37 9±9 8	20 1±7 1	180 0±47 9
Significance p	<0 001	<0 001	<0 001	<0 02	<0 001

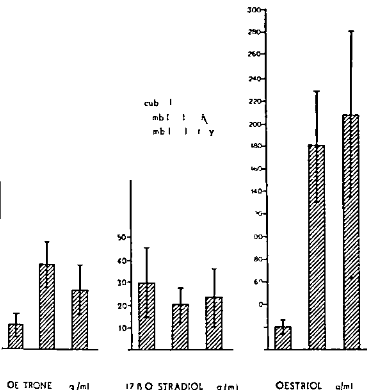


Fig 2 Plasma steroids in the foetal and maternal circulation at normal delivery—oestrogens

our process follow complex sex steroid changes a mechanism similar to that occurring in the ep (7) whereby oestrogen dominance could be olved in prostaglandin synthesis (3) thereby in asing the sensitivity of the myometrium to ytocin (14)

Although the precise mechanisms preceding the iversion of non progressive to progressive rine activity remain uncertain there is evidence dynamic changes in oestrogen metabolism occur g in association with parturition but it is proba that others are so transient or localised that they nain undetected in peripheral sampling

ACKNOWLEDGEMENTS

We are grateful to the volunteers who participated in this study and to Upjohn Limited for their support

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ble II *Concentrations of sex steroid hormones (ng/ml) in maternal and foetal circulations at elective sarean section (n=3)*

an and range

	Progesterone	17 hydroxy progesterone	Oestrone	Oestradiol	Oestriol
ntal vein	150 (177–186)	28 (7–66)	15 (10–22)	26 (9–48)	25 (11–38)
nbilical vein	440 (370–5_0)	3 (19–45)	27 (25–30)	13 (6–19)	209 (172–23?)
nbilical artery	377 (311–470)	23 (19–77)	26 (19–31)	16 (10–23)	243 (170–402)
noral artery	215 (180–760)	363 (11–84)	14 (17–16)	76 (17–39)	47 (13–104)
rine vein	393 (108–880)	46 (9–96)	15 (10–21)	4? (2_–77)	81 (40–106)

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Submitted for publication March 2 1977

Ian Craft
Academic Department of Obstetrics and Gynaecology
Royal Free Hospital
London N W 3
England

Acta Obstet Gynecol Scand 57 125–126 1978

ELECTRICAL POTENTIAL DIFFERENCE ACROSS THE MID TERM HUMAN PLACENTA

J Štulc J Švihovec J Drabkova J Stříbrny J Kobilková I Vido and A Doležal

From the Department of Pharmacology Faculty of Pediatrics and Department of Anaesthesiology and Resuscitation and 1st and 2nd Clinic of Obstetrics and Gynecology Faculty of General Medicine Charles University Prague Czechoslovakia

tract Electrical potential difference across the mid 'n human placenta was recorded during hysterotomy average value registered was 2 7 mV (S E of in=0 4 mV n=7) fetus negative From this value and concentrations of Na K Ca Cl and inorganic sphate in maternal and fetal plasma the possible isms of net transport from mother to fetus are rred It is concluded that of the above ions only the sport of Na is compatible with simple diffusion

material exchanged between mother and fetus he placenta must cross the placental barrier The vement across the barrier may be effected by ious mechanisms (9)

'he growing fetus accumulates inorganic ions s implies that there is a net flux of ions across placental barrier from the maternal to the fetal Of the ions taken up by the fetus Na K Ca Cl inorganic phosphate are accumulated at by far highest rates (4) Therefore only these ions will urther considered

he mechanisms by which the net flux of ions oss the placenta takes place are not known but ain inferences in this respect could be made n the values of the electrochemical potential rence across the placenta

he most simple mechanism of ion transport oss the placenta would be simple diffusion down electrochemical potential gradient The con trations of K Ca and inorganic phosphate in l plasma however are significantly above those aternal plasma the concentrations of Na and Cl he two sides of the placenta are approximately same (? 8) From this it follows that the net flux ese ions across the placenta cannot proceed by simple diffusion unless there is an electrical potential difference across the barrier providing the necessary driving force

An electrical potential difference across the placenta (p d) exists in many animal species (5 7 9) In humans at term no p d significantly different from 0 mV was detected (6) However the recordings of the p d across the human term placenta may not pertain to earlier stages of pregnancy The tissue separating maternal and fetal blood in the human placenta becomes highly attenuated with aging of the placenta (1 3) and the electrical resistance of the barrier is likely to decrease at the same time It is therefore possible that a p d across the human placenta exists in earlier stages of fetal development but that it disappears with advancing pregnancy For this reason we have measured the p d between maternal and fetal blood at mid pregnancy

METHODS

The recordings were performed in 7 women undergoing legal abortion by hysterotomy The reason for abortion was rubella in 6 women and schizophrenia in one woman The ages of the conceptuses estimated from the date of the last menstruation ranged from 15 to 22 weeks the average fetal weight was ?90 g (S E M =37 g)

The p d was recorded with a Tesla BM 483 microvoltmeter connected to the maternal and fetal blood through a pair of calomel electrodes and a pair of agar bridges (Portex 00 nylon tubing filled with agar saturated KCl solution) The agar bridges were inserted into the maternal cubital vein and into the umbilical artery of the fetus through guiding hypodermic needles The bridges were sterilized before use The fetus remained in the uterus during the recording The values obtained were corrected for the asymmetry of the electrodes

RESULTS

In all instances the fetal blood was negative with respect to the maternal blood The values of the p d obtained ranged from 0 8 mV to 3 7 mV with an average value of 2 7 mV (S E M =0 4 mV) There was no correlation between the p d and the length of pregnancy

DISCUSSION

The present recordings demonstrate that a p d does exist in humans However except for Na the p d observed cannot account for the net flux of the ions from mother to fetus The fetal side of the placenta being electronegative Cl and inorganic phosphate move up the electrical potential gradient In the case of K and ultrafiltrable Ca the p d would have to be 7 2 mV and 3 7 mV (fetus negative) respectively for the ions to be in equilibriaum across the placenta (The equilibrium potentials were calculated from the concentrations of K (8) and ultrafiltrable Ca (2) in maternal and fetal plasma using the Nernst equation) Since the p d observed is below these values the force of the electrical potential gradient driving K and Ca into the fetus is lower than the oppositely directed force represented by the concentration gradient

Of the ions considered only the net flux of Na across the placenta is compatible with simple diffusion For the other ions a non diffusional presumably active mechanism of transport across the placenta has to be assumed

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Submitted for publication March 16 1977

J Štulc
Dept of Pharmacology
Faculty of Pediatrics
Albertov 4
128 00 Prague 2
Czechoslovakia

Acta Obstet Gynecol Scand 57 127-128 1978

INTRAUTERINE DEATH DUE TO INFECTION WITH GROUP B STREPTOCOCCI

G Bergqvist G Holmberg T Rydner and V Vaclavinkova

om the Departments of Pediatrics St Goran Hospital and Obstetrics and Gynaecology Sabbatsberg Hospital Karolinska institutet and the Department of Obstetrics and Gynaecology St Erik Hospital Stockholm Sweden

ract During the 6-year period 1970-1975 5 cases of intrauterine death caused by group B streptococcal ·tion were seen in two obstetrical departments in the kholm area During the same period 17638 infants · born in the two departments and in 117 cases in erine death occurred Hematogenous spread of the tion from the mother was the most likely cause in the es This figure should be compared with a carrier rate ·-?0% in pregnant women in the Stockholm area

ng the last decade there have been several re s on neonatal group B streptococcal infections from the United States and from various ıtries in Europe (2 3 6 7 8) *The spectrum of* infections varies considerably from simple .nces such as low grade omphalitis to severe c conditions with a high mortality (3 9) The lren suffering the so called early type have lly contracted the infection in connection with ery and the same bacteria could then be iso- from the genital organs of the mother (3 6 7 However this bacterium seems to be very non in the urogenital organs both in pregnant n nonpregnant women (1 4 5) But the possi of group B streptococci causing intrauterine ı and abortion is less well documented al h Hood et al referred to it in 1961 in one of arliest papers on group B streptococcal infec We have observed some cases in Stockholm h we thought it of interest to report

MATERIAL AND METHODS

g the six year period 1 1 1970-31 12 1975 altogether l infants were born at two maternity clinics in Stock Among them were 117 cases of late intrauterine all of which have been fully reviewed An autopsy performed in all cases by a pathologist and bac ogical specimens were taken regularly from the *infants* for instance from cerebral tissue cardiac placental tissue etc

RESULTS

In altogether 24 cases bacterial infection seems to have contributed to the fetal death The bacteriolog ical composition of these cases is shown in Table I No case of Listeria was found

Regarding the group B streptococcal infection three infants were small for their gestational age None of them were born before term The five group B streptococcal infants probably died one to four days before delivery The time between membrane rupture and delivery was less than four hours in all the five streptococcal cases and in two *cases only 30 and 45 min respectively*

DISCUSSION

Group B streptococci as well as enterococci were common The same finding has been made by Hood *et al (8) who isolated group B streptococci from* the brains of 11 out of 113 dead fetuses or stillborn infants The spread to infants with massive infesta tion was probably hematogenous as the mothers had no signs of ascending infection However Overall (10) has pointed out the probability of group B streptococci penetrating intact membranes

Baker at al (1) calculated the risk of an infant of a group B streptococci carrier mother contracting an infection to be around 1% They considered the risk of intrauterine death to be small putting the overall risk of intrauterine death due to infection at

Table I

Streptococci group B	5
Streptococci group D (enterococci)	10
E coli	5
Other Gram neg rods	4
Total	24

only 0 13% and the risk of intrauterine streptococcal group B death at only 0 028% This should be compared with a carrier rate of 15–20% in pregnant women in the Stockholm area (4 5) a figure 500–700 times higher Thus the occurrence of sporadic cases of intrauterine death due to group B streptococcal infection hardly warrants general screening programs for group B streptococcal carriers among pregnant women However in individual cases with previous group B streptococcal infection (intrauterine or neonatal) we keep the mother under observation during pregnancy to detect if she is a carrier

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Submitted for publication April 4 1977

V Vaclavinkova
Dept of Obstetrics and Gynecology
Sabbatsberg Hospital
Stockholm
Sweden

Acta Obstet Gynecol Scand 57 129–131 1978

MATERNAL MORTALITY IN SWEDEN 1955–1974

Stefan Fianu

From the Department of Obstetrics and Gynecology Sabbatsberg Hospital Karolinska Institutet Stockholm Sweden

stract A survey of the causes of maternal death in eden during the years 1955–74 is presented 296 cases ere autopsy has been performed in 94% have been ·iewed 219 have been classified as obstetrical deaths 1 77 as non-obstetrical During the period an almost form lowering of the maternal death rate occurred The olanation is a probable improvement in the quality of medical care given in the hospitals and the antenatal ncs

the past childbirth was a time of great anxiety l danger The earliest London records tell us that he seventeenth century one woman in 40 lost her at the time of delivery A century ago the risk one fifth and the maternal mortality rate was ressed as being 5 per 1 000 registered live or lbirths

'he maternal mortality rate in Sweden according arly Goteborg records was 4% between 1856– (at the Carolus Dux Maternity in Goteborg) er 1876 the risk at delivery had fallen to 0 61% s figure remained almost unchanged for 60 years it was not until 1936 that a steady and dramatic started

MATERIAL

material studied consisted of 296 cases from the years 5–74 It was divided into 10-year periods and correla was made with the official number of deliveries lished by the National Board of Health and Welfare ble I)

he maternal mortality rate is expressed as a proportion oned on the number of deliveries and the number of ernal death within a month of delivery of a liveborn nt or a stillborn foetus at least 35 cm in length Mater deaths following abortion were not included

he study was based on a direct analysis of the hospital ords of all maternal deaths in Sweden during the 20-year period 1955–74 The figures for the number of de liveries have been obtained from the official statistics of the National Board of Health and Welfare

The hospital records were obtained by kind cooperation of the heads of the respective departments

Autopsy was performed in 94% of the cases with classification according to the complication considered to be the principal cause of death

RESULTS

During the two 10-year periods 2 222 909 women gave birth with 296 maternal deaths (Fig 1) This *figure shows that the mortality rate which started* to fall in 1935 has continued its downward trend up to the present day After dividing the causes of maternal death into two groups—obstetrical and non obstetrical—there were 219 obstetrical and 77 non obstetrical causes of death

Obstetrical causes of death

(Table II)

Infection was the cause of maternal death in about 11% of cases and was so with the same relative frequency during both the 10-year periods despite

Table I *The maternal mortality rate during the periods studied*

	Number of deliveries	Maternal mortality *n*	Per 100 000 deliveries
1955–64	1 083 4 6	210	19 3
1965–74	1 139 483	86	7 5
1955–74	2 2?2 909	296	13 3

Table II *Obstetrical causes of death*

Years	Infection		Pre eclampsia		Eclampsia		Haemor rhage		Thrombo-embolism		Air embolism		Amnio. embolism	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%
1955–64	17	11 2	16	10 5	29	19 1	45	29 6	9	5 9	7	4 6	13	11
1965–74	7	10 4	7	10 4	12	17 9	12	17 9	2	3 0	1	1 5	15	2[illegible]
1955–74	24	11 0	23	10 5	41	18 7	57	26 0	11	5 0	8	3 7	28	[illegible]

Table III *Non obstetrical causes of death*

Years	Appendicitis	Ileus	Anaesthesia	Heart failure	cerebral haemorrhage	Aortic aneurysm	Pneumonia	Malignancy	Suicide	Varius	Tot.
1955–64	1	10	3	12	8	2	3	6	2	11	[illegible]
1965–74	1	2	2	2	1	3	3	2	1	[illegible]	19
1955–74	2	12	5	14	9	5	6	8	3	13	[illegible]

the fact that the absolute number of deaths from sepsis has diminished by more than 50%

Pre eclampsia was the cause of death in 10 5% of cases there was no difference in the relative frequency between the two periods The decrease was only numerical even in this group

Eclampsia was considered to be the principal cause of death in 19% there was no relative difference between the two 10 year periods

Haemorrhage The proportion of deaths at[illegible] able to haemorrhage was 26% there seems to be slight relative and numerical decrease in the se[illegible] period regarding this category

Amniotic embolism was diagnosed in 9% [illegible] the first 10-year period and in 2[illegible]% during the se[illegible] ond The diagnosis was established histologica[illegible] 9 of the 13 cases in the first period and in 1[illegible] of 15 cases during the second period Some of[illegible]

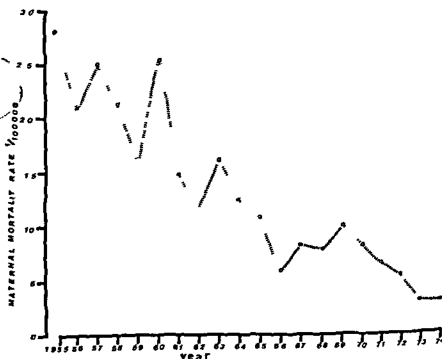


Fig 1 Maternal mortal[illegible] Sweden 1955–74

of	Inversion of uterus		Total number	
	n	%	n	%
)5	0	—	152	100
19	1	1 5	67	100
19	1	0 5	219	100

s classified as haemorrhage during the first od might therefore have suffered from un nosed amniotic embolism

upture of the uterus was diagnosed in 12% was no significant difference between the two ods

obstetrical causes of death

le III)

e has been a great variation in the cause of h especially during the first period including ic accidents suicides virus infections etc The difference between the two periods seems to slight decrease concerning ileus and heart fail

DISCUSSION

women in Sweden give birth in hospital (over The number of maternity departments d by specialists in obstetrics and gynaecology ncreased during the last 10 years During the ds studied 87 2% of all deliveries took place ich departments However there was no icant difference in the rate of maternal mortal tween maternity departments headed by or not headed by specialists in obstetrics and ology (Table IV) The explanation is probably that most hospitals have had units for intensive care during the last 10-year period The absolute decrease in maternal mortality during the last 10-year period includes all causes of death As there has been no change in nutritional standards during the time of observation and the access to medical care has been almost the same over the last 20 years the explanation could be higher quality of the medical care given in the hospitals during the last 10 years

Especially the decreased number of cases of heart failure and ileus seems to prove this assumption

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Submitted for publication March 21 1977

Stefan Fianu
Department of Obstetrics and Gynecology
Sabbatsberg Hospital
S-113 82 Stockholm
Sweden

IV *Maternal mortality rate during the studied periods*

	Maternity departments without specialist in obst & gynec			Maternity departments headed by specialist in obst & gynec				Maternal mortality	
		Maternal mortality			Maternal mortality				
	Number of deliveries	n	Rate/ 100 000	Number of deliveries	n	Rate/ 100 000	Total number of deliveries	n	Rate/ 100 000
64	146 143	3?	21 9	937 ?83	178	18 9	1 083 426	210	19 3
74	138 608	11	7 9	1 000 875	75	7 4	1 139 483	86	7 5
74	284 751	43	15 8	1 938 158	253	13 0	2 2?2 909	296	13.5

Acta Obstet Gynecol Scand 57 133–135 1978

EFFECT OF GENERAL AND LOCAL ANAESTHESIA ON BLOOD LOSS DURING AND AFTER THERAPEUTIC ABORTION

Birger R Møller Jørgen Trier Hansen and Søren Mommsen

From the Surgical Out patient Clinic Aarhus Kommunehospital Aarhus Denmark

ict The blood loss occurring during therapeutic on performed under local and general anaesthesia he postoperative bleeding was measured in 60 y women in the first trimester of pregnancy The its were 20–30 years old (mean age 24 3 years) all nulliparae They were divided into three equal s according to the duration of pregnancy In each 10 patients underwent abortion under general thesia and the remaining 10 under local anaesthesia cases cervical dilatation by the Hegar method and m aspiration were used and all operations were rmed by the same surgeon General anaesthesia was ed with atropine and thiopental and maintained with tion of a 2 1 mixture of nitrous oxide and oxygen mall doses of thiopental and pethidine Local thesia consisted in paracervical blockade produced ection of 1% lidocaine adrenaline The blood loss l) was smallest in the 7th and 8th weeks of preg under both local and general anaesthesia and in d with the gestational age In all three groups the loss during operation under general anaesthesia was twice as large as under local anaesthesia There no difference in the postoperative bleeding under and general anaesthesia It is concluded that local thesia has several advantages Paracervical block rovides a rapid and reliable anaesthesia which is iate for most patients The costs delays and compli is of general anaesthesia are avoided Local thesia is well suited for out patients and the blood reduced to a minimum

veral studies on therapeutic abortions (14 15 7 18) widely varying complication rates have reported A variety of techniques for the ination of pregnancy and different types of sthesia have been employed During the last years nearly all authors have expressed the that cervical dilatation by the method of Hegar vacuum aspiration are safe procedures well d for out patient intervention

most series studied the operation was ormed under general anaesthesia but some reports (2 10 13) seem to indicate that the blood loss is smaller when local anaesthesia is used However in these studies the operations were performed by various staff members the blood loss was measured only during the operations and postoperative bleeding was not recorded As in some of these studies the patients constitute a heterogeneous group as regards age parity and duration of preg nancy the results are difficult to compare In the investigation presented here an attempt was made to collect a homogeneous groups of patients The blood loss was measured both during the operation and postoperatively and all the operations were performed by the same surgeon In this way it will be possible to compare the blood losses occurring when either general or local anaesthesia is used

MATERIAL AND METHODS

The patients studied were 60 healthy women in the first trimester of pregnancy undergoing elective therapeutic abortion Their ages ranged from 20 to 30 years and aver aged 4 3 years all were nulliparae The gestational age was determined clinically by the obstetrician on the basis of the menstrual history and estimation of the size of the uterus The patients were divided into three equal groups according to the duration of pregnancy as follows Group I duration less than 9 weeks Group II 9–10 weeks Group III 11–12 weeks In each group 10 patients un d rwent operation under general anaesthesia while local anaesthesia was employed in the remaining 10

Informed consent to the procedure was obtained from all the patients concerned

In all cases the procedure was cervical dilatation by the method of Hegar and vacuum aspiration This procedure has previously been described in detail by others (10 16) All the operations were performed on out patients by the same surgeon who had wide experience in this interven tion

All the patients were premedicated with diazepam 10 mg intravenously General anaesthesia was induced with

Table I *Blood loss during and after therapeutic abortion in 60 first trimester pregnancies*

Duration of pregnancy	Bleeding during operation (ml)				Postoperative bleeding (ml)			
	Local anaesthesia		General anaesthesia		Local anaesthesia		General anaes[illegible]	
	Mean	Range	Mean	Range	Mean	Range	Mean	Ra[illegible]
Under 9 weeks	21 9	15–30	38 0	24– 50	20 0	10–30	18.2	[illegible]
9–10 weeks	40 9	32–60	70 6	50– 90	35 0	25–50	31.5	[illegible]
11–12 weeks	77 7	70–95	145 0	110–200	49 0	30–65	54.5	[illegible]

intravenous injections of atropine 0 5 mg tubocurarine 3 mg and a small dose of thiopental 250–300 mg Small doses of pethidine 20–40 mg were administered as an analgesic The anaesthesia was maintained by sufficient additional thiopental in a few cases small doses of suc cinylcholine and inhalation of a 2 1 mixture of nitrous oxide and oxygen

Local anaesthesia consisted in paracervical blockade produced by 1% lidocaine adrenaline 10+10 ml The solution was injected into the paracervical tissue at the junction of the cervix and vagina in the lateral fornices at the 4 and 8 o clock positions The needle was inserted 10 mm into the tissue the syringe was aspirated and then 10 ml of the solution was injected on either side of the cervix

Postoperatively all patients were given methyl ergonovine maleate (Methergine®) 0 2 mg intramuscu larly

As already mentioned the blood loss was measured both during the operation and postoperatively

Blood loss during operation

During the suction the uterine contents were collected in a container After the operation a known amount of 5% sodium hydroxide was added and 24 hours later the opti cal density of the resulting alkaline haematin so ution was measured The result was compared with the patient s venous blood treated similarly The principle of this was described by Hallberg & Nilsson (8) and modified by Kasonde & Bonnar (9) Blood loss on drapes and sponges was minimal and therefore disregarded

Postoperative bleeding

The patient s blood loss after the operation was de termined by collecting sanitary towels (Molnlycke A/S Copenhagen) in buckets and extracting the haematin us ing sodium hydroxide in a known amount as mentioned above The haemoglobin loss was calculated from the extinction of the resulting alkaline haematin solution and the volume of the extract The postoperative bleeding was then estimated from the haemoglobin concentration and compared with the patient s venous blood treated similar ly

RESULTS

The results are summarized in Table I Mann Whitney s test was used in the statistical analysis In all three groups the blood loss during operation under general anaesthesia was nearly tw[illegible] as under local anaesthesia i e the di[illegible] highly significant ($p<0\ 05$)

In contrast to this the postoperati[illegible] showed no statistical difference with the [illegible] of anaesthesia In both types of anaes[illegible] blood loss was smallest in the 7th and 8[illegible] pregnancy and increased with the gesta[illegible]

Under both types of anaesthesia the [illegible] lasted slightly more than 5 min but ne[illegible] 10 min The duration of general anaes[illegible] about 10 min and never more than 15 m[illegible]

In most cases postoperative bleed[illegible] within 1–2 days in all cases it stopped [illegible] days The procedure did not give rise to [illegible] plications in particular no clinical signs [illegible] dometritis salpingitis or parametritis [illegible] haemorrhages requiring blood transfus[illegible] uterine perforations or cervical ruptures [illegible] countered

DISCUSSION

Considerable blood losses may occur [illegible] therapeutic abortion performed in the first [illegible] of pregnancy Dvorak et al (5) described the [illegible] lem of patients requiring transfusion after [illegible] tic abortion and Eaton (6) reported [illegible] ranging from 100 to 500 ml during su[illegible] tion of the pregnant uterus

It is well documented (4 1[illegible]) that hal[illegible] potent uterine relaxant associated with [illegible] blood loss during legal abortion Some [illegible] 10) have suggested that halothane is [illegible] indicated as an anaesthetic agent for this [illegible] because of the enhanced blood loss associa[illegible] its use Cyclopropane anaesthesia has [illegible] reported to be followed by heavy bleed[illegible] the authors therefore concluded that it sh[illegible] avoided for this procedure

he method of general anaesthesia used in this dy is reported to be safe and well suited for brief ɔgical operations (4) Thiopental can de ss uterine contractility (7) and thus perhaps in ase the blood loss Clinical experience suggests nitrous oxide in non hypoxic concentrations little inhibitory effect on uterine contractility and in one study (4) it is reported that the ding is smaller than in any other form of general esthesia

'he local anaesthesia used in our study was pro- ed by lidocaine with added adrenaline renaline has a vasoconstrictive action which de s the absorption of local anaesthetics and re es blood flow in the tissues One observation) indicates that lidocaine is a potent vasocon ctor when applied to the arteries in the pregnant rus and that this agent stimulates the smooth scles of the pregnant uterus in vitro (3) In addi lidocaine seems to potentiate the stimulating ct of adrenaline (1) All these effects seem to rease the blood loss during the operation The erence in the blood losses during general and al anaesthesia observed in our study is in keep- with the findings just mentioned

n conclusion it may be said that the choice of eral or local anaesthesia appears to have a defi effect on the amount of blood loss during elec therapeutic abortion We found that the blood s under local anaesthesia was only one half of t occurring under general anaesthesia The eding was well tolerated by all the patients who re young and healthy women but the occurrence profuse haemorrhage may very well be hazard to a patient with a limited cardiovascular re ive

Ve find that local anaesthesia has several vantages Paracervical blockade provides a rapid l reliable anaesthesia which is adequate for most ients The costs delays and complications as iated with general anaesthesia are avoided cal anaesthesia is well suited for out patient in vention and the blood loss is reduced to a nimum

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Submitted for publication Nov 3 1976

Birger R Møller
Miltonsvej 11
DK-8270 Højbjerg
Denmark

Acta Obstet Gynecol Scand 57 137–139 1978

DOXYCYCLINE (VIBRAMYCIN®) IN PELVIC INFLAMMATORY DISEASE

Halvard Gjønnæss and Eirik Holten

From the Department of Gynecology and Obstetrics Aker Hospital and the Bacteriological Laboratory Aker Hospital Oslo Norway

ract Using standardized laparoscopy technique fluid aspirated from the pouch of Douglas from the Fallo- tubes and from ovarian cysts in 85 cases with clinical nosis of pelvic inflammatory disease (PID) The con ration of doxycycline in the aspirates was measured oral ingestion of 200 mg of doxycycline (Vibramy) A therapeutic level was achieved in the tubes and in ian cysts within a few hours and on continuation of reatment these values followed the plasma concentra closely still being within the therapeutic range 24 's after the final dose The clinical effect was excel 94% (60/64) of the cases with verified PID being d by doxycycline

re are numerous microorganisms capable of sing pelvic inflammatory disease (PID) They frequently not identified presumably due to inical difficulties and recent reports indicate a tively high frequency of anaerobic bacteria (6) roles of *Mycoplasma* and *Listeria* are still un ain

etracyclines are often used in treatment of PID ycycline (Vibramycin ®) has been claimed to e certain advantages over other tetracyclines ause it is so well absorbed has a slow akdown in serum and has a low frequency of effects (4 5 9) Its antibacterial effect *in vitro* aerobic and certain anaerobic bacteria has been nd to be higher than that of other tetracyclines although the number of resistant strains of erobes seems to be increasing (1) Beside the *in* o antibacterial effect the *in vivo* effect also de ds upon the drug concentration at the site of ction The crucial point in the treatment of PID resumably the concentration of antibiotic ob- iable within the lumen of the Fallopian tubes hough the penetration of doxycycline into vari tissues has been the subject of many investiga ns (8 9 10) we have not found any report on investigation of the intratubal doxycycline concen tration

The aim of this study has been to determine the concentration of doxycycline in tubal fluid com pared with the plasma levels to observe the time interval from oral ingestion of standardized doses until a therapeutic level of doxycycline is reached within the Fallopian tubes and the maintenance of this level after cessation of treatment

MATERIAL AND METHODS

Diagnostic laparoscopy was performed in 85 women with a clinical diagnosis of pelvic inflammatory disease (PID) This diagnosis could not be verified in 21 cases Twenty two patients had ovarian cysts 9 of them in combination with PID The frequency of gonococci in the cervix was 18% in those cases where cervical secretion was ex amined bacteriologically In cases of gonorrhoea the symptoms of PID developed after therapeutic abortion in 2 cases and postmenstrual in 2 (Table I)

On admission doxycycline treatment was initiated whenever PID was suspected with 200 mg orally followed by subsequent daily doses of 100 mg Within 1–2 days laparoscopy was performed and using the standard tech nique fluid was aspirated from the Fallopian tubes and from the pouch of Douglas The latter fluid was consid ered to be of tubal origin in cases of tubal patency From hydro/pyo-salpinges and from ovarian cysts fluid was obtained through long cannulas inserted transabdominally

Table I *Bacteriological findings in 85 patients with a clinical diagnosis of pelvic inflammatory disease*

Age (years)	*n*	Not per formed	Gonor rhoea	Non specific microbes
16–20	32	7	5	0
21–30	43	23	3	17
30–45	10	5	1	4
Total	85	35	9	41

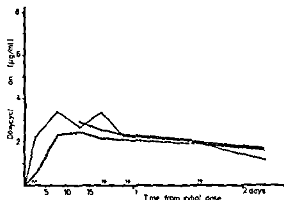


Fig 1 Doxycycline concentration in the Fallopian tubes ( ) capillary blood plasma (—) and venous blood plasma ( ) after standard oral treatment

under visual guidance Plasma was obtained from finger tip capillary blood The recordings were made only once from each patient

The concentration of doxycycline was determined using standard paper disks from AB Biodisk Solna Sweden according to the method of Jalling et al (7) Antibiotic medium No I (Difco) was used and the test bacterium was *Bacillus cereus* ATCC 11778 Peritoneal fluid from non treated cases had no effect on this bacterium

Because of technical error 3 cases had to be omitted from the total series of 85

RESULTS

Doxycycline in tubal fluid

Within 10 hours from the primary dose of doxycycline the plasma and tubal concentrations averaged 2 5 µg/ml or more (Fig 1) Continued treatment revealed concentrations averaging 2 µg/ml The mean tubal and plasma concentrations then

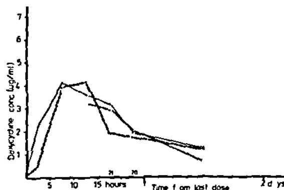


Fig 2 Doxycycline concentration in the Fallopian tubes ( ) capillary blood plasma (—) and venous blood plasma ( ) related to the last dose of doxycycline given orally

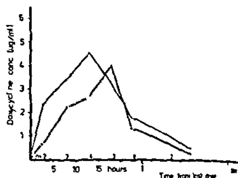


Fig 3 Doxycycline concentration in ovarian cys... and capillary blood plasma (—) related to the last do... doxycycline given

showed identical levels throughout the observ... period Even though the mean values were ide... cal the individual cases did not always show g... good correlation The correlation coeffic... 0 68–0 80–0 61–0 57–0 56–0 57–0 4... for the re... spective time intervals in Fig 1 The presence... absence of active inflammatory disease di... seem to influence these results After 4 h... nearly all of the patients had received their ... dose of 100 mg doxycycline After the trea... was discontinued there was a parallel and ... decrease in tubal and plasmal conc... (Fig 2)

In 7 cases of tubal occlusion the doxycy... concentration was recorded in tubal and perito... fluid separately (Table II) These values ... almost identical so that our working hyp... sis—that of peritoneal fluid being represent... of the tubal exudate in the case of tubal p... cy—seems justified

Doxycycline in ovarian fluid

In 22 patients fluid was aspirated from ovarian ... and examined for doxycycline concentr... (Fig 3) The mean concentrations in ova... and plasma showed similar correspondence ... plasma and tubal levels

Clinical effect

In 4 patients with PID doxycycline treatm... discontinued because of doubtful or poor e...

Table II *Mean doxycycline concentrat... tients with tubal occlusion*

Tubal fluid	1 3 µg/ml
Peritoneal fluid	1 4 µg/ml
Plasma	1 8 µg/ml

ne of them was diagnosed 3 months post partum d in one case the PID appeared after a menstrual riod In none of them were specific bacteria und They all responded promptly to ampicillin The 9 patients with gonorrhoea were all appar tly cured by doxycycline In none of the patients l treatment have to be discontinued because of e effects

DISCUSSION

e penetration of the antibacterial agent to the tual inflammation sites is of vital importance for anti infectious effect For doxycycline the isma tubal and ovarian concentrations showed rapeutic levels within a few hours from the intial se (Figs 1 3) The maximum concentrations re recorded within 10 hours after the initial dose is given The mean doxycycline level from then showed only a minor decrease throughout the servation period demonstrating therapeutic vels more than 24 hours after the final doxy cline dose

The doxycycline concentrations in the tubal fluid the majority of cases exceeded the values given minimum inhibitory concentration against merous aerobic and anaerobic microbes (2) The cellent clinical effect in 94% (60/64) of the cases th PID indicates that the doxycycline concentra ns found in the tubes were adequate even *in vivo*

The rapid resorption of doxycycline the h concentration and the achievement of an uilibrium between the plasma and tubal or arian concentrations indicate excellent penetra n of the drug into these organs Our observations in agreement with reports dealing with serum ncentrations after oral ingestion of 200 mg of xycycline (5) and on doxycycline penetration into her organs (8 10)

ACKNOWLEDGEMENTS

are indebted to Mrs M Vangdal for technical as- tance and also to our colleagues in the gynaecological department who kindly participated in the collection of the material

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Submitted for publication Aug 31 1976

Halvard Gjønnæss
Kvinneklinikken
Aker Sykehus
Oslo 5
Norway

Acta Obstet Gynecol Scand 57 141–147 1978

THE INFLUENCE OF LOCALLY ADMINISTERED PROSTAGLANDIN E_2 AND $F_{2\alpha}$ ON UTERINE MOTILITY IN THE INTACT NON PREGNANT HUMAN UTERUS

J N Martin Jr M Bygdeman and P Eneroth

From the Department of Obstetrics and Gynecology Karolinska Hospital Stockholm Sweden

stract Clinical studies on the effect of locally ministered prostaglandin E_2 and $F_{2\alpha}$ on the sensitivity d reactivity of the non pregnant human uterus were formed in 16 volunteers With the use of the flaccid roballoon technique uterine recordings were made at quent intervals throughout the menstrual cycle As lit as 0 25 μg PGE_2 or 1 0 μg $PGF_{2\alpha}$ effected an increase uterine motility during most of the proliferative and retory phases of the menstrual cycle However a rked decrease in sensitivity and suppression of reactiv to either prostaglandin compound was observed ound ovulation Moreover an inhibition of uterine con ctility in response to PGE_2 but not to $PGF_{2\alpha}$ was noted ring active menstrual bleeding Circulating levels of rogen could be correlated generally with these uterine ponses Endogenous prostaglandins normally occur in secretory endometrium in levels compatible with the ount of exogenously administered prostaglandins ich elicited increased decreased or unchanged uterine tivity in this study These findings suggest that local staglandin E_2 and $F_{2\alpha}$ in concert with variable levels of culating estrogen may play important roles in the clic regulation of uterine motility during the menstrual cle

ce von Euler (7) reported in 1934 that seminal id contains relatively high concentrations of tent smooth muscle stimulatory agents called ostaglandins many investigators have under ken intensive studies in attempts to identify ysiological roles for these compounds in the mplex interplay of events which constitute the man reproductive process Areas of special in rest have been sperm transport sperm capa tation tubal function and fertilization itself More er in recent years there have been several ports investigating the myometrial response of the n pregnant human uterus to systemically ministered prostaglandin E_2 and $F_{2\alpha}$ (3 10 15) Attention has been focused in the regulation of uterine contractility around ovulation and during menstruation

It is well known that the non pregnant human uterus exhibits a characteristic general pattern of spontaneous activity which varies according to the different phases of the menstrual cycle It appears that estrogen generally exerts a predominantly stimulatory or at least facilitatory effect in contrast to the depressive myometrial effect of progesterone (4 9 13)

Whereas *in vitro* work has suggested that PGE compounds generally inhibit the contractility of human myometrial strips (1 16) reports from *in vivo* work indicate that intravaginal intramuscular or intravenous PGE cause uterine stimulation One exception is during the concurrent intravenous administration of oxytocin and vasopressin when inhibition has been reported following vaginal administration of extract of human seminal fluid (6) Prostaglandin $F_{2\alpha}$ consistently stimulates uterine myometrium both *in vitro* and following systemic *in vivo* administration (1 3 10 15 17) The signifi cance of uterine recordings made following the systemic administration of prostaglandin is how ever difficult to interpret with regard to uterine sensitivity since the amount of compound reaching the uterus is small and variable

The present investigation was performed to study the sensitivity and reactivity of the non pregnant human uterus to the intra-uterine administration of physiological amounts of PGE_2 or $PGF_{2\alpha}$ during the various phases of the menstrual cycle and to compare these responses with circulating estrogen and progesterone levels

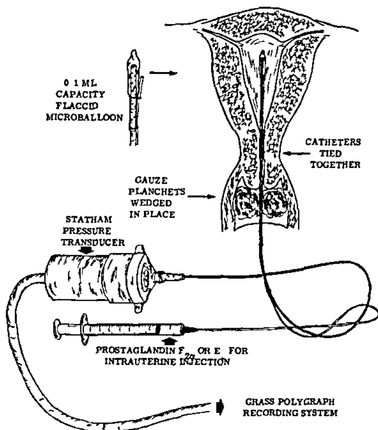


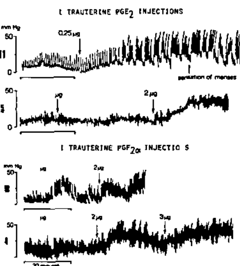
Fig 1 The figure illustrates the [illegible] system with the flaccid [illegible] Prostaglandin E_2 and $F_{2\alpha}$ were [illegible] istered into the uterine cavity through 0 66 mm polyethylene catheter tied to recording line

PATIENTS AND METHODS

Sixteen women were chosen for this investigation All volunteers had a history of regular menstrual cycles and were found to have normal gynecological examinations Eleven women were nulliparous and 5 were multiparous All contraceptive agents except condom were terminated at least one month prior to the beginning of the study [illegible] tus was prohibited 24 hours before each recording Ovulation was confirmed by a biphasic basal temperature chart and by a rise in serum proge[illegible]one There were 83 recording sessions including five control sessions All patients were recorded at least once during the proliferative and secretory portions of the cycle as well as during menstruation and around the expected time of ovulation Six patients received only PGF_2 and 6 received only PGE_2 4 patients received both compounds during single recording sessions for comparison

Uterine contractility was recorded by means of a flaccid microballoon (0 1 ml capacity made by London Rubber Ltd) tied to a polyethylene catheter and connected to a Statham pressure transducer and a Grass polygraph The fluid filled air tight system was calibrated before each recording At the volunteer s first visit the direction and length of the cervico-uterine canal was determined by sounding the uterus The microballoon tipped catheter was inserted gently through the endocervical canal at least 1 cm beyond the internal os The catheter was secured in place by wedging several gauze planchets into the vagina and around the catheter line prior to removal of the speculum (Fig 1) The patient then gently assumed [illegible] supine position and remained quietly there for the [illegible] tion of the 2–3 hour recording session Baseline [illegible] activity was recorded for at least 20 minutes prior [illegible] prostaglandin instillation The prostaglandin $F_{2\alpha}$ [illegible] was prepared immediately before testing by [illegible] solution (5 mg/ml) with physiological saline to achieve [illegible] concentration of 5 or 20 μg $PGF_{2\alpha}$ per ml The [illegible] solution was prepared by diluting concentrated stock [illegible] buffered saline to achieve a concentration of either [illegible] μg PGE_2 per ml Small volumes were frozen immediately [illegible] and maintained at −20°C until use At each recording session increasing amounts of the GPE_2 or $PGF_{2\alpha}$ [illegible] (0 1–1 6 ml) were administered into the uterine cavity [illegible] means of a pre filled 0 66 mm polyethylene catheter [illegible] to the recording line The time interval between [illegible] usually allowed uterine contractility to return to [illegible] levels Uterine stimulation or inhibition was considered significant whenever basal tonus was elevated more [illegible] mmHg or if there were an obvious change in the [illegible] and/or frequency of contractions A single [illegible] volunteer acted as control during 5 recording sessions spaced throughout the menstrual cycle each time [illegible] ing up to 1 6 ml normal saline injected into the [illegible] cavity

Serum for progesterone and estradiol 1 β [illegible] ments was collected and stored at − [illegible]°C until [illegible] radioimmunoassay (RIA) Progesterone in 1 0 ml of [illegible] was determined with the antibodies and the basic [illegible] dure of Micromedic Diagnostic Inc (Progest[illegible]



Uterine recordings showing the uterine response to and $PGF_{2\alpha}$ during the preovulatory phase (4–11 before ovulation)

immunoassay kit) The purity of the progesterone ard (Applied Science) was acertained by thin layer as–liquid chromatography as well as by determina of its molar absorbancy index (REF) in absolute ol The purity of ^{3}H labeled progesterone used for onitoring of procedural losses was checked with the chromatographic methods Estradiol 17β in 1 0–2 0 serum was determined after extraction (2×10 ml ether Mallinckrodt) and chromatography on columns of Sephadex LH 20 in the solvent ne methanol 95/5 (v/v) ^{3}H labelled estradiol (New nd Nuclear) 5000 dpm was added to serum prior to tion The estradiol fraction (8 5–15 5 ml effluent) ssayed with antibodies from New England Nuclear 044) The RIA procedure recommended by the facturer was followed The purity of the estradiol ard (Applied Science) and of ^{3}H labelled estradiol hecked in the same way as for progesterone

RESULTS

non pregnant human uterus responded in a acteristic way to the intra uterine instillation of or $PGF_{2\alpha}$ according to the phase of the strual cycle The patterns of response could be ped arbitrarily into four phases the preovula periovulatory postovulatory and menstrual rence to the time of uterine recording in this r therefore was based upon the number of days re (−) or after (+) the estimated date of ovula

Preovulatory phase

From the cessation of menstruation until approximately 4 days before ovulation the intra uterine instillation of small amounts of either PGE_2 or $PGF_{2\alpha}$ generally resulted in a relatively rapid stimulation of uterine contractility The effect of injected prostaglandin upon uterine motility during this phase could be characterized by a gradual rise in uterine tonus accompanied by increased amplitude of contraction No evidence of inhibition was observed As little as 1 0 μg of either compound usually effected a response and stimulation was sustained or enhanced with larger doses of prostaglandin (Fig 2) Quantitatively less PGE_2 than $PGF_{2\alpha}$ appeared to effect a definite response in those patients who received both compounds during a single recording session

Periovulatory phase

Fig 3 illustrates the relative lack of uterine response to the intra uterine administration of PGE $PGF_{2\alpha}$ respectively around the time of ovulation In contrast to the previously seen stimulatory response of the preovulatory uterus higher doses of prostaglandin around ovulation induced little change from a typically low amplitude high frequency regular baseline pattern In several patients given higher doses of PGE_2 preceded or followed by single instillations of $PGF_{2\alpha}$ neither compound consistently elicited an obvious stimulatory nor inhibitory response The period of relative non response could extend as long as 4 days after the estimated time of ovulation but thereafter blended into the next phase

Postovulatory phase

Several days after ovulation until the onset of menstrual bleeding spontaneous uterine activity under the influence of progesterone characteristically evolved into increasingly irregular less frequent and higher amplitude contractions similar to those seen late in the prelabor phase of term pregnancy Locally administered PGE_2 or $PGF_{2\alpha}$ during this portion of the menstrual cycle invariably resulted in stimulation The overall stimulatory response was qualitatively and quantitatively less marked than early in the cycle Particularly following PGE_2 injections the stimulatory response early in the post ovulatory was manifested by an increase in the duration and intensity of contractions while an elevation of uterine tonus was not always a part of the

A ta

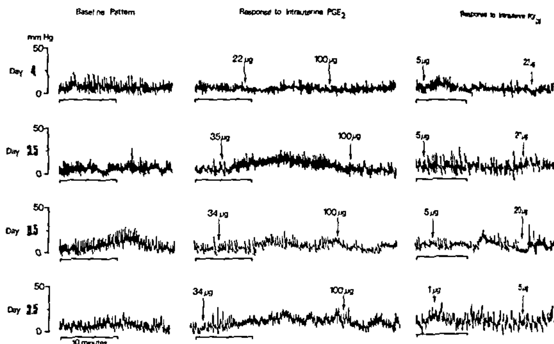


Fig 3 Relative uterine unresponsiveness to even large intra uterine instillations of PGE_2 and $PGF_{2\alpha}$ administered to the same patients during the periovulation (4 days before to 3½ days after ovulation)

effect Later in this phase an increase in resting uterine tonus was noted to occur as part of the response to increasing amounts of PGE_2 and $PGF_{2\alpha}$ and this was accompanied sometimes by mild discomfort As demonstrated in Fig 4 doses of $PGF_{2\alpha}$ equal to those of PGE_2 seem to effect greater responses in contrast to the pattern observed during the preovulatory phase

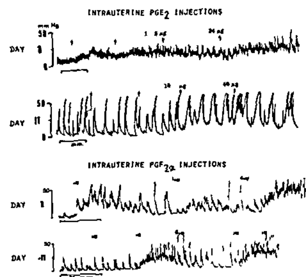


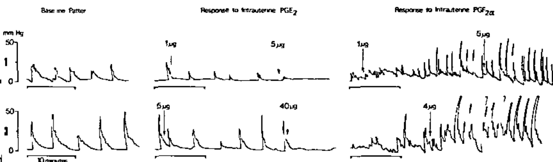
Fig 4 Uterine response during the late secretory phase (6–11 days after ovulation) to intra uterine instillations of PGE_2 and $PGF_{2\alpha}$

Menstrual phase

The only inhibitory response to the intrauterine [illegible] jection of prostaglandin occurred following [illegible] instillation during menstrual bleeding The [illegible] to $PGF_{2\alpha}$ in contrast continued to be [illegible] stimulatory As shown in Fig 5 uterine [illegible] ity was inhibited by small amounts (1 5 µg) [illegible] and more strongly depressed by larger doses [illegible] for periods lasting up to 20 min while the [illegible] uterine injection of 1–5 µg $PGF_{2\alpha}$ elicited a [illegible] nite stimulatory response

Hormonal levels and uterine reactivity

Based upon basal body temperature [illegible] blood sampling for progesterone at each [illegible] uterine recording all 16 study subjects [illegible] during the test menstrual cycles Estrogen [illegible] addition to progesterone values were [illegible] each recording session for the last 5 [illegible] studied and were consistent with [illegible] ported date The mean estrogen values [illegible] in Fig 6 with 95% confidence limits The [illegible] serum estrogen levels achieved during the [illegible] strual cycle occurred just prior to ov[illegible] coincided in time with the period [illegible] ine reactivity to locally administered [illegible] $PGF_{2\alpha}$ was most depressed Moreover the [illegible] mean levels of circulating estrogen [illegible]



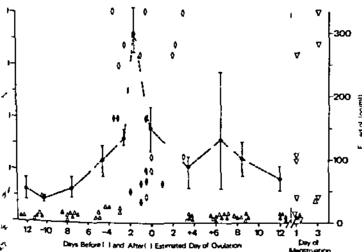
5 Uterine recordings from two patients during the struation Of note is the inhibitory effect of PGE_2 and timulatory effect of $PGF_{2\alpha}$ in the same patient

ovulatory phase corresponded to the time of t easily demonstrated reactions to PGE and $_{2\alpha}$ Later in the postovulatory phase during second peak of estrogen the reactivity to both taglandin compounds appeared muted

DISCUSSION

efficacy of the flaccid microballoon technique the recording of uterine contractility as de bed by several investigators has become as well pted as the open end method (3 4) The oballoon method avoids problems involving ructive secretions which can be encountered open end catheters lacking sponge tips and is especially more suitable than the continuous flow system when studying the effect of intra uterine administration

Baseline variations in uterine contractility throughout the menstrual cycles of the 16 women studied were comparable to the characteristic pat terns described previously by others using a variety of recording techniques (4 9 13) Even though all recordings exhibited features of these general pat terns a wide variation was noted between patients A variation in uterine sensitivity to prostaglandins during the menstrual cycle *in vivo* following systemic administered prostaglandin has not been demonstrated (3 10 15) However following in travenous administration both PGE_2 and $PGF_{2\alpha}$



6 Summary of threshold values for locally ad stered PGE_2 and $PGF_{2\alpha}$ in 16 patients during the strual cycle together with the mean estrogen values 95% confidence limits for 5 patients Threshold stimulation dose PGE_2 △ $PGF_{2\alpha}$ ▲ Highest dose ad ministered without effect PGE_2 □ $PGF_{2\alpha}$ ■ The dose causing initial inhibition sometimes followed by stimula tion PGE_2 ▽

are very rapidly transformed into biologically less active metabolites and thus the amount of the compounds eventually reaching the uterus is small and variable

The present investigation demonstrates that the response of the non pregnant human uterus to locally administered PGE_2 and $PGF_{2\alpha}$ is dependent upon the phase of the menstrual cycle Stimulation by both prostaglandin compounds usually an increase in uterine tonus was observed from the cessation of menstruation until approximately 4 days before ovulation During the periovulatory phase a relative insensitivity to as much as 20 μg of intra uterine PGF_2 or 100 μg PGE_2 was noted in all study subjects

Thereafter until the onset of menses the uterine response to E and F prostaglandin was characterized by a more tempered increase in contractional amplitude and activity than by an outright increase in uterine tonus These results are in accordance with those we have reported earlier (12 13) Finally during menstrual bleeding uterine contractility could be depressed by locally administered PGE_2 in contrast to the consistently stimulatory effect of $PGF_{2\alpha}$ The intra uterine instillation of physiological saline to the control patient failed to effect any change in uterine contractility at any time during the menstrual cycle

The present results are compatible with the earlier findings by Embrey as quoted by Pickles et al (14) Embrey found that intra uterine administration of as little as 0 5 μg $PGF_{2\alpha}$ stimulated increased uterine contractility in 2 patients on days 24 [illegible]nd 26 of their menstrual cycles The only *in vivo* [illegible]s investigating the effect of locally ad[illegible]istered prostaglandin E_2 upon the nonpregnant human uterus have been reported recently by Toppozada and his co workers (18 19) These investigators also found a stimulatory response following the intrauterine instillation of PGE_2 in the pre and postovulatory phases of the menstrual cycle However they reported an inhibitory response to PGE_2 during the periovulatory phase in contrast to the lack of response observed in our study Another major point of difference was the much higher doses of PGE_2 necessary to elicit uterine responses in the Toppozada studies One reason might be the different PGE_2 preparation used

The levels of $PGF_{2\alpha}$ as its major metabolite (15 keto 13 14-dihydro-PGF_2 in the human endometrium during the menstrual cycle has been measured recently by Green & Hagenfeldt [illegible] chromatography mass spectrometry tech[illegible] A high concentration of 15-keto-13 14-[illegible] $PGF_{2\alpha}$ was found during the luteal or post[illegible] portion of the cycle little if any of the [illegible] could be detected in the endometrium [illegible] time of ovulation Downie et al (9) [illegible] concentration of primary prostaglandins [illegible] PGE_2 and $PGF_{2\alpha}$ increased progressively [illegible] luteal phase of the cycle At least during the luteal portion of the cycle the endometrial [illegible] corresponded to the exogenous amounts [illegible] $PGF_{2\alpha}$ which elicited a uterine response [illegible] present study

Pickles earlier bioassay work demonstrated the primary prostaglandins are present in the [illegible] endometrium throughout the menstrual c[illegible] although secretory endometrium has a high [illegible]tent of $PGF_{2\alpha}$ with an increased PGF [illegible] ratio and menstrual fluid contains about 10 [illegible] more $PGF_{2\alpha}$ than is found in secretory endometrial curettings (14)

The present findings do suggest that PGE [illegible] PGF compounds may play important physiological roles in the cyclic regulation of uterine m[illegible] ing the menstrual cycle During menstruation [illegible] turbance in the relative balance of these com[illegible] with increased PGF and/or a deficiency of P[illegible] originally suggested by Pickles may be an im[illegible] factor involved in the increased myometrial [illegible] and pain noted in patients suffering from p[illegible] dysmenorrhea especially since treatment [illegible] prostaglandin biosynthetase inhibitors such [illegible] domethacin reduce uterine activity and [illegible] well as ease the pain for the pat[illegible] (11)

Periovulatory relative insensitivity to both [illegible] and $PGF_{2\alpha}$ corresponded to the highest [illegible] estrogen achieved during the menstrual cy[illegible] the highest sensitivity was before and af[illegible] struation when the estrogen levels [illegible] Myometrial reactivity to prostaglandin [illegible] may at least partially be under hormonal [illegible] similar to what has been reported for [illegible]

It has been speculated that the high pro[illegible] E concentration in human seminal fluid [illegible] ence uterine contractility after intercourse [illegible] facilitate passive sperm transport The [illegible] tively low sensitivity of the myometrium [illegible] ovulation to PGE_2 indicates that other [illegible] may be responsible to the statistically [illegible] correlation observed between low hu[illegible]

l PGE concentration and infertility (2) To help her evaluate the role of prostaglandins in human oductive functions additional careful studies needed to study the interrelated effects of vagi y administered upon the human cervix cervical sus and fallopian tubes

ACKNOWLEDGEMENT

work was supported by the WHO Expanded Pro- ime of Research Development and Research Train

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Submitted for publication March 1? 1977

Marc Bygdeman
Dept of Obstetrics and Gynecology
Karolinska Hospital
S-104 01 Stockholm 60
Sweden

Acta Obstet Gynecol Scand 57 149–159 1978

HUMAN OVARIAN TUMOURS HETEROTRANSPLANTED TO NUDE MICE

Stig Kullander Alf Rausing and Claes Trope

From the Department of Gynaecology and Obstetrics and the Institute of Pathology University of Lund Allmanna Sjukhuset Malmo and the Tornblad Institute University of Lund Lund

ract ?? different human ovarian tumours were rotransplanted subcutaneously to female nude When small tissue pieces were used 10 out of 16 ours grew Subcutaneous injections of suspended our cells were made to 11 mice all failed Metastatic filtrative growth was never seen in the mice observed up to 25–40 days Material from each tumour was planted to four separate sites in two mice The suc ful grafts largely retained the original morphological ures As measured with H_3-thymidine incorporation A synthesis was also similar in the original tumours the growing grafts This animal *in vivo* model might be ly informative for the study of *inter alia* fundamental ogy chemotherapy and irradiation of ovarian tu rs

investigation and treatment of human ignant tumours can be facilitated by a suitable rimental animal model Previous techniques been based on transplantation of malignant e to immunologically privileged sites e g the ister cheek pouch and the anterior chamber of eye in rats and guinea pigs (4 5) or to experi ital animals immunologically deprived after n (1) However all these tumour host systems disadvantages In some total chromosomal ?es shift and in others signs of interspecies ridization were observed (7 12 15)

ne potential model is the heterotransplantation human tumours into nude mice The nude ise is a mutant homozygous for the recessive osomal gene nu These mice were first noted by icsson & Cattanach (1962) Later Pantelouris 8) found that homozygous mice are born with a thymus giving an immunological incompe e that permits the acceptance of a wide range of rografts Rygaard & Povlsen (1969) succeeded ransplanting a human colon adenocarcinoma to de mice A number of human tumours have e been successfully transplanted (2 9 13 16 18 20 22) Chromosome analyses of tumours n early and late passages (19) isoenzymes and immunological studies have shown that human malignant tumours transplanted to nude mice can maintain their original human properties (20)

Only occasional studies of a few ovarian tumours have been published (8) These tumours offer special interesting features because of their vary ing histopathology hormone-dependency and antigenic properties This report is concerned with the acceptance growth and histology of a number of grafted human ovarian tumours We wished to know whether different types of ovarian tumours were transplantable in nude mice and whether they would conserve the morphological characteris tics of the original tumours The study also included a comparison of transplantability of solid tumour fragments and cell suspensions and of the rate of DNA synthesis in the tumour tissue before and after grafting

MATERIAL AND METHODS

5–6 weeks old female nude mice (nu/nu) C 57/B1/6j/ Bom/nu were used Originally the heterozygous mice were supplied by G L. Bomholtgard Ltd Ry Den mark and later bred in our own colony We used clean but not fully pathogen free conditions which allowed an

Table I *Histological classification and number of tumours studied*

Histopathology	No of cases studied
A Epithelial cancer	
Serous	4
Mucinous	4
Endometrioid	3
Undifferentiated carcinoma	8
B Sex cord stromal tumour	
Granulosa cell	1
C Lipoid cell cancer	1
D Benign tumours	
Cystadenofibroma	1

Table II *Tumour material and results of grafting*
0=no tumourtake +=successful tumourtake A=ascites C=cystfluid

Case	Age of patient	Histology of tumour	Clinical stage	Previous tumour treatment	Cell suspension from solid tumour	Cells from cyst fluid or ascites	Solid tumour fragments	Orig[illegible]
1	76	Serous	III	Irradiation	0	–	–	Metastasis
2	44	Serous	III	Irradiation	–	0	+	Primary [illegible]
3	69	Serous	III	Irradiation	0	0	–	Primary [illegible]
4	68	Serous	III		0	0	(+)	Primary [illegible]
5	57	Mucinous	I*a*		0	–	0	
6	60	Mucinous	II*a*		0	–	+	Primary [illegible]
7	54	Mucinous	II*c*		–	0	+	Metastasis
8	61	Mucinous	III	Irradiation	0	–	0	
9	71	Endometrioid	I*a*	Cytostatic drugs	0	–	0	
10	52	Endometrioid	I*c*	Irradiation	0	–	–	Metastasis
11	62	Endometrioid	I*c*		–	–	0	
12	76	Undiff ca	IV		–	0	+	Primary [illegible]
13	76	Undiff ca	IV		–	0	+	Metastasis
14	64	Undiff ca	IV		–	–	+	Metastasis
15	65	Undiff ca	I*b*	Irradiation	0	–	0	
16	73	Undiff ca	III		–	–	–	Primary [illegible]
17	56	Undiff ca	II*c*		–	+ (A)	+	Metastasis
18	60	Undiff ca	IV		–	–	+	Primary [illegible]
19	57	Undiff ca	III		–	+ (C)	+	Metastasis
20	62	Granulosa	III		0	0	+	Metastasis
21	29	Lipoid	I*b*		0	–	0	
22	73	Cystadeno-fibroma	–		–	–	(+)	Primary [illegible]

average life span of 4 months The mice were fed ordinary laboratory food and water *ad lib* The coarse sawdust bedding was not sterilized

Tissue fragments from ovarian tumours were obtained at laparotomy Ascites was obtained at laparocentesis or laparotomy and cystic fluid was obtained at aspiration of ovarian cysts Within one hour the solid tumour material was cut into small pieces measuring [illegible] with scissors in Parker 199 (SBL Stockholm) [illegible] In a number of cases some of the small pieces [illegible] brought into a suspension of single cells with the [illegible] stainless steel mesh Cells from cystic fluid and [illegible] were obtained by low speed centrifugation

The technique for incorporation of labelled [illegible] into tumour DNA *in vitro* was described in [illegible] Håkansson & Trope (1973) The cell suspension [illegible] bated for one hour with tritiated thymidine [illegible] centration of 2 MCi/ml All tests are performed [illegible] The cell suspensions are then washed with phosphate [illegible] fer and the cells are precipitated with cold [illegible] acid which extracts nucleosides and nucleotides [illegible] amount of thymidine incorporation and the DNA [illegible] of each sample is measured and an expression [illegible] lated to estimate the amount of incorporated [illegible] per DNA in the sample This expression has a [illegible] form to make statistical calculations easier

The formula is

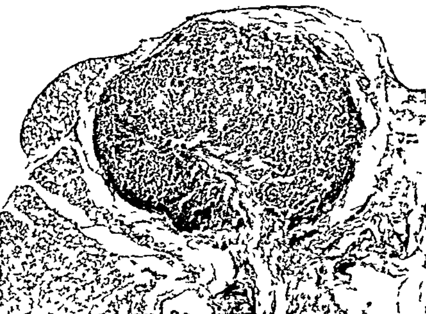
$$a = 100 \log \frac{(\text{c p m}) \times 10^{4}}{(\text{AES}) \times (\text{DNA})}$$

Where (c p m) is the number of counts registered [illegible] is the c p m registered with automatic external [illegible] ization and (DNA) is the amount of DNA [illegible] expressed in arbitrary units but corrected with a [illegible] curve

Under sterile conditions two nude mice [illegible] subcutaneously with four pieces 2×[illegible] mm of the [illegible] tumour tissue and often also two mice with [illegible]

Table III *Successfully grafted tumour fragments*

Case	Histological differences between primary and transplanted tumours when fragmented pieces are used	*Takes/ Attempts*	Serial transplants/ *takes*
2	Slight	5/8	4/3
4	Great (Grafts under resorption?)	2/8	1/0
6	None	6/8	2/1
7	None (In one graft lymphoid tissue was found)	3/8	0
12	None	4/8	0
13	None–slight	4/8	0
14	None	4/8	1/0
17	None	2/8	0
18	None	4/8	3/2
19	None	3/8	0
20	None	3/8	0
22	None	1/8	0



/ Implant of poorly differentiated ovarian carcinoma 17) Thin fibrous capsule surrounding implant and is septa radiating from it ×70

volume of 0 1 ml of Parker 199 (SBL Stockholm) n cystic fluid cells or ascites cells were used 2–6 on cells were injected subcutaneously Two pieces or njections were put on each side of the mouse over the and hind leg regions respectively The animals were rved daily and tumour appearance was evaluated y third day by palpation A minimum size of 4×4×4 was considered a sign of acceptance and growth This ared approximately 25 to 40 days after inoculation n the animals were killed the acceptance rate among grafts was recorded The tumour grafts were taken the inoculation sites and some samples of the urs were then brought into cell suspension for DNA nesis determination The remaining pieces were fixed ouin s solution for paraffin wax embedding section hematoxylin eosin staining and microscopic exami n

le histological picture was compared with that of the nal tumour tissue In some cases the tumour graft also transplanted to subsequent generations of the le mice The host sometimes died or became sick other causes and then had to be sacrificed earlier rial for DNA synthesis study and histological exami on could also be collected in several of these cases e 1 surveys the number of human ovarian tumours ed and their original histological picture

RESULTS

le II shows patient s age histology clinical e of the tumour and previous treatment also the ults of grafting

When *small tissue fragments* were used 10 out of 16 human tumours grew as localized tumours with a minimum size of 4×4×4 mm at one or more of the transplantation sites In six of these ten xenografts the samples came from peritoneal meta stases Two samples from metastases did not grow (cases 1 and 10 they had received previous irradia tion) In four of the ten xenografts the samples came from primary tumours Four samples from primary tumours failed to grow (One of these pa tients had previously been irradiated case 3) From a total of four previously irradiated patients only one tumour (no 2) grew after transplantation

When cell suspensions from ascites cyst fluid or solid tumours were used the takes were poor Only 2 transplantations were successful (cases 17 and 19) both undifferentiated cancers and with cells from ascites or a cyst respectively Eleven trials with cell suspensions made from solid tumour tis sues were negative

Tumour inocula could usually be recognized as established after 14 days and grew as well circumscribed tumours The tumours were not in filtrating into the skin or underlying tissue They could easily be observed measured and biopsied No metastases to lymph nodes or other organs were observed Serial growth was possible in one serous

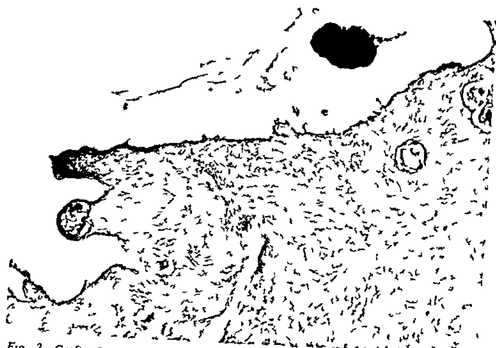


Fig 2 Graft of serous papillary cystadenocarcinoma (case 4) showing a mass of connective tissue without tumour cells Some calcified spherules are seen and small calcified bodies in the human tumour ×70

one mucinous and one undifferentiated tumour The serous tumour was serially transplanted for up to four passages (Table III) There were no histological differences between the primary and the serially transplanted tumours

The microscopic picture of the grafts in cases agreed well with the human donor tumour Table III Figs 3–4 In two cases 4 and 7 localized tumours were recognised there histological difference between some of the



Fig 3 A human mucinous adenocarcinoma (case 6) ×180



4 The same tumour as in Fig 3 grown in the mouse
)

ts and the donor tumour One (case 4) serous illary cystadenocarcinoma showed a mass of nective tissue without tumour cells in two ts Some calcified spherules were seen similar to small calcified bodies in the human tumour Fig 2 shows the appearance of this tissue in the mouse

In one case of mucinous cystadenocarcinoma (no 7) three implants grew No tumour was found in



5 Papillary and solid adenocarcinoma in human An sional lymphocyte is seen around tumour structure e 19) ×180

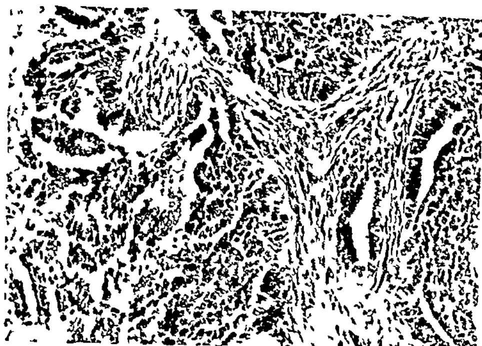


Fig 6 Implant of tumour seen in Fig 5 Lymphocyte reaction even slighter than in human ×180

one only a lump of loose connective tissue with organized lymphatic tissue

The growth rate of the heterotransplanted tumour grafts was variable One tumour (no 4) grew very slowly and never surpassed 4×4×4 mm up to the time of the animal s death In cases 2 and 18 one take in each showed a considerable growth measured 10×10×15 mm when the animal was killed In case 19 spontaneous regression was observed in one out of 3 successfully grafted pieces

In the successful implantations the grafts

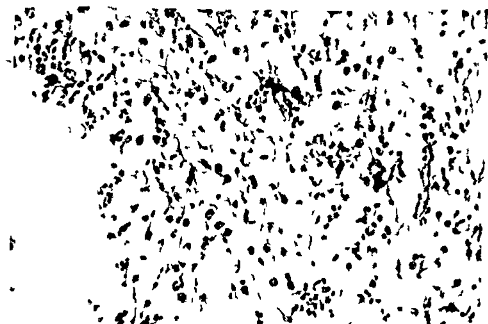
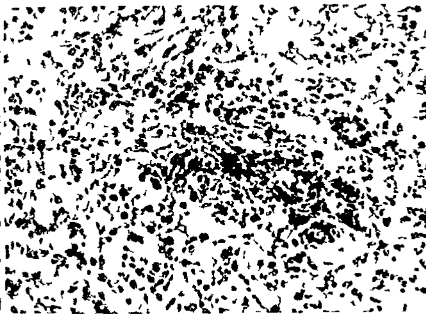


Fig 7 Diffusely growing anaplastic carcinoma of human Aggregate of lymphocytes to the left (case 13) ×180



8 Implant in mouse of tumour seen in Fig 7 Similar
›logical picture and focal lymphocyte aggregate
0

wellcircumscribed surrounded by a condensed r of connective tissue in all probability derived n host tissue Fibrous septa were generally seen in the tumours They radiated from the capsule 1) Thin walled vessels were seen within the ous septa They could often be traced to similar els in the capsule and were probably derived n the host Quite extensive necrosis was often ı within parts of the implant but this was prob related to poor vascularization and further erations of the same implant showed good vital of the cells

enerally there was no or only slight inflam ory reaction in the growing graft tumour tis The stroma trabecules were without reaction s 5 and 6 case 19) In a diffusely growing ana tic carcinoma (case 13) however the human ue contained many focal aggregates of lymphos as did the implant in the mouse (Figs 7 8)

/e also compared the rate of DNA synthesis in tumour tissue before and after grafting to see ther there were any differences in proliferation acity of the primary tumour and the heteroısplants Table 4 shows the result of the incor ation studies of tritiated thymidine into DNA

In six cases (nos 2 12 13 14 17 18) all the accepted mouse tumours had a significant DNA synthesis that is the tumours retained their proliferative capacity There was no difference in DNA synthesis between the accepted tumours in the same animal and there was no difference between the primary human and the xenograft

In cases 4 and 7 the primary tumours showed a significant DNA synthesis but those xenografts of these mice (4*b* and 7*a*) that histologically consisted only of a mass of connective or lymphoid tissue had no DNA synthesis Patients 19 and 20 showed no differences in the histological pictures between the primary tumour and the xenografts but the accepted grafts did not show any DNA synthesis In patient 6 all the tissue fragments were accepted in one mouse and all the grafts showed a DNA synthesis which did not differ from one another and did not differ from the DNA synthesis of the primary tumour cells When transplantation with suspended cells from cyst fluid was made two grafts were accepted but neither of them had any DNA synthesis

Fast growing mouse tumours (cases 2 and 18) showed a high H^3 thymidine uptake thus showing a high DNA synthesis and these tumours had a high



Fig 9 Serous cystadenofibroma of human (case 22) ×70

acceptance rate These were from primary human tumours

Slow growing mouse tumours (cases 4 20 and 22) which did not show any uptake of H³ thymidine often came from primary tumours or metastases with originally low uptake The be cystadenoma (case 22) showed practica growth or DNA synthesis but conserved its h ogy the tumour graft measured only 3x3x1 (Figs 9–10)



Fig 10 Mouse implant of tumour seen in Fig 9 ×70

IV *DNA synthesis in successfully grafted original tumour material and grafts*

ırks successful tumourtake O=marks no tumourtake DNA synthesis of the primary tumours and of the suc lly transplants expressed in *a* values

DNA synthesis of primarytumour										
Cyst cells	Ascites cells	Cell susp (solid tumour)	DNA synthesis of the transplants							
			a				*b*			
–	–	306 84				24? 36	305 02			
		285 65		O	●	276 71	304 14	●	O	
			347 88	●	●	? 6 36	341 92	●	O	
			273 55			231 46	344 75			
			a				*b*			
–	–	48 65		O	O			O	●	
		85 76		O	O			O	●	
			a				*b*			
–	46 30	76 48	75 08			49 9?				
	75 46	8? 66	63 36	●	●	37 51	–	O	●	–
	(no takes)		27 49	●	●	17 74	–	O	●	–
			31 42			1? 16				
			a				*b*			
–	–	86 03								49 72
		89 83	–	O	●	–		O	●	58 23
			–	O	O	–		O	●	68 39
										60 34
			a				*b*			
–	–	143 25	198 34			117 73				86 79
		18? 34	209 58	●	●	115 03	–	O	●	99 59
				O	●	?08 36	–	O	O	–
						210 37				
			a				*b*			
0	0	9 30					18 62			17 78
		35 10	–	O	O	–	16 99	●	●	22 65
			–	O	●	79 72	–	O	●	35 40
						97 58	–			47 86
			a				*b*			
	–	190 87				18 67				219 20
		186 36	–	O	●	179 67	–	O	●	218 69
			173 2?	●	●	163 49	–	O	O	–
			174 79			161 46				
			a				*b*			
0	123 53	145 09								111 93
	1?4 55	136 70	–	O	O	–	–	O	●	113 94
			–	O	O	–	–	O	●	114 03
										131 83
			From ascites							
			c				*d*			
			151 84				105 1?			96 62
			155 13	●	O	–	105 96	●	●	101 16
			–	O	O	–	–	O	O	–
			a				*b*			
0	0	247 85				218 8?				21? 44
		21? 95	–	O	●	214 83	–	O	●	212 38
			–	O	O	–	–	O	●	212 95
										214 38

Table IV (Cont)

Case	DNA synthesis of primary tumour: Cyst cells	Ascites cells	Cell susp (solid tumour	DNA synthesis of the transplants						
				a				b		
19	135 07 142 32	0	189 93 192 80							
				–	○	●	–	–	○	●
				–	○	○	–	–	○	●
				From cystfluid						
				c				d		
				–	●	○	–	–	●	○
				–	○	○	–	–	○	○
				a				b		
20	0	0	50 32 45 22							
				–	○	●	–	–	○	●
				–	○	○	–	–	○	●
				a				b		
22	0	0	3 13 21 68							
				–	○	○	–	–	○	●
				–	○	○	–	–	○	○

DISCUSSION

10 out of 16 human ovarian tumours were successfully heterotransplanted when using tissue fragments This is a very good acceptance rate But tissue fragments from each patient were transplanted at 8 sites to 2 mice therefore the total graft acceptance figures are not so impressive Out of a total of 128 tissue fragments 38 were accepted ome of our accepted grafts had a slightly different icroscopical pattern from the primary tumours his is not surprising The patterns within a single primary ovarian tumour can be numerous and highly different The growth rate was different also in one case spontaneous regression was noted

We used the same nude mice strain as Giovanella & Stehlin (1974) but in contrast to them we did not find any sign of local invasion or metastases to lymph nodes Also in contrast to them we succeeded in only two cases with heterotransplantation when cell suspension was used

However Giovanella et al used human tumours that had been cultured in several passages before heterotransplantation It is possible that when cells are cultured in vitro there is a selection of cell clones with increased capacity to grow and [illegible] metastases in the nude mouse

Preliminary LDH isoenzymes analysis of [illegible] venous blood several weeks after our [illegible] showed that the original human tumour [illegible] picture was mirrored in the mouse blood [illegible] observation supporting the view that orig[illegible] man tumour properties are maintained [illegible] der further study

Grafting of solid tissue fragments was [illegible] successful than injection of suspended ce[illegible] fragments possess their own vascular bed [illegible] has only to connect to blood vessels of [illegible] order to ensure survival of the graft B[illegible] cells have to elicit the neoformation of [illegible] from the surrounding tissues

In our material all the serous tumours [illegible] grade and high stage Of the mucinous [illegible] three out of four were low stage but [illegible] endometrioid tumours were low grade and [illegible] stage Of undifferentiated tumours [illegible] were high stage all eight being high grade [illegible] ly high stage and high grade human tumours [illegible] greater chances to be accepted as xenografts [illegible] seems easier to succeed in heterotra[illegible] when using material from metastases rather from primary tumours

Only one of the tumours from six previously
ated patients grew (no 2) This tumour had an
remely high incorporation of thymidine in spite
the irradiation treatment which means that the
nour cells had a high proliferation rate probably
reasing the possibilities for successful het
otransplantation The other tumours in previ
ly treated patients had a low DNA synthesis
e irradiation and the cytostatic drugs might di
tly or indirectly have influenced cellular multi
ation DNA synthesis and the possibilities of
se damaged cells growing in the nude mouse
There is usually high DNA synthesis in fast
wing tumours In most cases the proliferative
pacity of human tumours was maintained in the
epted grafts Two cases (nos 19 and 20) showed
difference in the histological picture between
mary tumours and xenografts but the accepted
nours did not show any DNA synthesis

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Submitted for publication Jan 24 1977

Claes Trope
Department of Obstetrics and Gynecology
Malmo General Hospital
?14 01 Malmo
Sweden

Acta Obstet Gynecol Scand 57 161–164 1978

POSTOPERATIVE IRRADIATION AND CHEMOTHERAPY IN PATIENTS WITH ADVANCED OVARIAN CANCER

C Welander K E Kjørstad and P Kolstad

From the Gynaecological Department the Norwegian Radium Hospital Oslo Norway

tract Two groups of patients with stage III ovarian inoma were selected for a randomized clinical trial first group consisted of 157 patients who had radical gery at their first laparotomy the second group con d of 145 patients with inoperable disease The aim of trial was to compare the results of maximum external avoltage irradiation 5000 rads to a large abdominal l with the results of a reduced dose 3000 rads im liately followed by chemotherapy with an alkylating nt (Thio-tepa) In none of the groups did maximum otherapy prove superior to the schedule of a reduced combined with chemotherapy The less costly and saving combined treatment was better tolerated than liation alone Histological tumour type did not influ the prognosis in these advanced cases where spread found outside the true pelvis

importance of radiotherapy in the management varian malignancy is controversial (1 3 6 7 9 Increasing use of chemotherapy with promising ilts in many cases has also created doubt as to ther radiotherapy has a place in the treatment of type of disease

ı a previous report (5) an attempt to assess the ›t of preoperative irradiation in patients with ›erable disease was made The present study erns the role of postoperative irradiation and notherapy for patients with advanced ovarian er with spread outside the true pelvis

MATERIAL AND METHODS

ı 1968–73 456 patients with malignant epithelial urs of the ovary stage III were admitted to the Nor an Radium Hospital Of these 30? were selected for a ›ective randomized study and divided in two groups e first group hereafter referred to as the control › consisted of 157 patients who had complete re d of all visible tumour tissue at the first laparotomy wing surgery they received 3000 rads supervoltage irradiation to a large abdominal field 20×.6 (8) cm extending from the symphysis to the T_1 region The radiation was given in 18 fractions of 167 rads through parallel opposed anterior and posterior portals over approximately four weeks The kidneys were shielded after 2000 rads The patients were then randomized either to continue the external irradiation to a midplane abdominal dose of 5000 rads or to chemotherapy with triethylene thiophosphoramide (Thio-tepa) The initial dose schedule was 60 mg in divided doses over 6 days followed by another 60 mg administered in the same way after a rest period of two weeks Maintenance therapy followed at lower doses usually 10–20 mg every second week Monitoring of chemotherapy was performed by weekly or bi weekly peripheral blood counts Lower limits allowed were haemoglobin 10 5 g/100 ml leucocytes ?000/ml platelets 100000/ml Kidney and liver function tests were taken before therapy started and later at monthly intervals A high protein diet anabolic steroids vitamins and if indicated blood transfusions were given during treatment

The second selected group referred to as the study group consisted of 145 patients with inoperable disease This diagnosis was based on either the findings at laparotomy (96 patients) or on clinical examination (49 patients) They received 3000 rads midplane supervoltage radiotherapy in the manner described above before a second look or primary operation was attempted

Approximately one third of the patients responded well to radiotherapy and could have a considerable bulk of tumour resected In another third parts of the primary and metastases could be removed and the last third had completely inoperable disease despite the irradiation given (5) Irrespective of the outcome of the post irradiation surgery the whole "study group" was then randomized to receive another 2000 rads to the same field as before or to have chemotherapy as outlined above

The distribution by histological tumour type is given in Table I Survival curves have been estimated according to the life table method and no patient was lost to follow up Separate survival curves were made for the five main histological tumour types but curves for the mesonephroid and undifferentiated tumours are omitted in the figures presented here as they were identical to the curves for the serous and endometrioid tumours

Table I

		Tumour type							
		Serous		Endometrioid		Mucinous		Other	
	No	No	%	No	%	No	%	No	%
Control group	157	84	54	26	17	28	18	19	11
Study group	145	84	58	26	18	8	6	27	18
Total	302	168	56	52	17	36	12	46	15

RESULTS

The 5 year survival for the total series of 302 patients was 16% (Fig 1) In Fig 2 the survival curves for the two groups are shown The difference in 5 year survival reflects only the bias in selection of the two groups Patients in whom it was possible to remove all macroscopic tumour tissue at the first laparotomy (control group) had a much better prognosis than patients with inoperable disease

No observable difference in survival was seen between patients that had a full course of radiotherapy up to 5000 rads compared with those that had only 3000 rads followed by chemotherapy (Figs 3 and 4) At all points in the graphs the standard errors overlap This applies to both the study group and control group 72 patients in the study group had no postoperative radiotherapy but chemotherapy instead The relation between histological tumour type and survival is shown in Figs 5 and 6 No differences were found between the tumours of different histology and the mesonephroid and undifferentiated tumours followed the curves for the serous type (Not shown in the graphs) As shown in Table I the majority of the mucinous tumours (28/36) belonged to the control group This may indicate that these tum[illegible] more resectable even when spread has o[illegible] outside the pelvis

DISCUSSION

The prognosis for patients with advanced ov[illegible] malignancies has changed little in the last [illegible] years In an attempt to achieve better tre[illegible] results both pre and postoperative rad[illegible] has been widely used (2 4 6 10 11 1[illegible]) In[illegible] new techniques and advanced equipment [illegible] makes it possible to deliver a high and evenly [illegible]buted dose the outlook for patients wi[illegible] outside the true pelvis is very poor Some t[illegible] obviously react to radiotherapy but the pr[illegible] of giving adequate doses in the abdomen ar[illegible] as the necessary shielding of the liver and k[illegible] will substantially limit the effects of ir[illegible] Very few patients that are left with recog[illegible] metastases outside the pelvis will survive [illegible] than 2–3 years and half of them will be dead [illegible] the first year of follow up

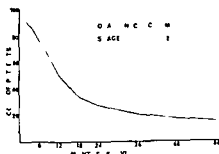


Fig 1 Survival curve for the whole group of 302 patients

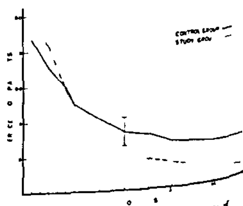
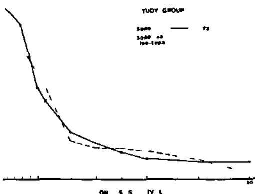


Fig 2 Survival curves for the two groups studied



3 Survival in the study group 73 patients with a full e of radiotherapy to 5 000 rads no chemotherapy 72 nts with 3 000 rads preoperative radiotherapy no perative radiotherapy but chemotherapy

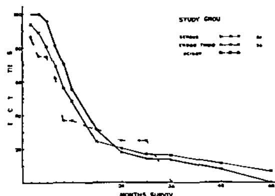
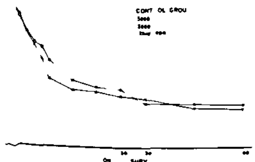


Fig 5 Survival in relation to tumour type Study group

ie present study was undertaken to compare esults of maximum postoperative radiotherapy those achieved by a combination of a reduced of irradiation combined with immediate che ierapy We had two reasons for combining therapy and chemotherapy Firstly in our ex nce preoperative radiotherapy makes it pos to remove both the primary tumour and stases in patients with inoperable disease in ximately one third of the cases (5) Therefore med wrong to deny patients with a poor prog the possible benefit of this kind of treatment ndly the necessary shielding when a large minal field is given greatly diminishes the to the usual sites of spread and the additional use of chemotherapeutic agents seemed logical The results of the present study show that max imum radiotherapy is not superior to a reduced dose of irradiation combined with an alkylating agent such as Thio-tepa This combination therapy saves time and eliminates many of the risks and incon veniences of radiotherapy In some centers radio-therapy in advanced ovarian cancer has been abandoned and treatment is based on single or multiple drug therapy (1 9) The 5 year survival rates achieved in the present study compare well with such treatment protocols The degree of pallia tion is harder to assess as each schedule has differ ent side effects The patients tolerated well external irradiation to a so-called large abdominal field up to 3 000 rads In many cases ascites was reduced and the general condition of the patients improved In the group receiving 5 000 rads the frequency of severe side effects was high with loss of weight electrolyte disturbances due to vomiting and diarrhea and lowering of serum proteins



Survival in the control group 77 patients with a full of postoperative radiotherapy to 5 000 rads no therapy 80 patients with 3 000 rads postoperative erapy followed by chemotherapy

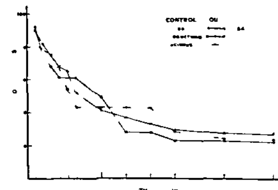


Fig 6 Survival in relation to tumour type Control group

Some authors feel that when the malignant process has spread outside the pelvis histological tumour types and degree of differentiation assume little prognostic significance (4 8) This agrees with the findings in the present study In our opinion the sites and extent of spread are of great importance In the future it will be necessary to reach an agreement upon a subdivision of stage III ovarian carcinomas

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Submitted for publication Feb [illegible]*7 1977*

K E Kjørstad
Department of Gynecology
The Norwegian Radium Hospital
Montebello
Oslo
Norway

Acta Obstet Gynecol Scand 57 165–168 1978

RELAPAROTOMY IN ADVANCED OVARIAN CARCINOMA

G Frick J E Johnsson T Landberg and M Snorradottir

From the Gynecologic Section Department of Oncology and the Department of Pathology University Hospital Lund Sweden

ract Patients with Stage III ovarian carcinoma were ed either with extensive initial surgery and postopera radiation therapy (17 patients) or with a less extensive al laparotomy postoperative radiation therapy and parotomy (19 patients) Better results were obtained ng the patients in the latter group

gery is the chief form of treatment used in rian carcinoma Bilateral salpingo oophor my and hysterectomy are the standard proce s utilized by the surgeon Varying opinions t however as to how radical the surgical sures should be in patients having advanced ours involving the peritoneum large vessels intestine Some authors recommend radical ery in order to remove as much of the tumour ossible (3 9) Others on the contrary stress the of dissemination of the tumour if the procedure lts in exposing large tumour masses and they ad recommend relaporotomy after radio- apy if possible and/or chemotherapy (5 6 7) 1?)

his article discusses the value of relaparotomy age III ovarian carcinoma

MATERIAL AND METHODS

tal of ?21 patients with ovarian carcinoma were re d to the clinic during the years 1971–73 Staging was using the FIGO classification (14) (Table I)

ment principles

primary operations were as a rule performed in the ological departments in the receiving area

ter diagnostic curettage surgery was performed if was not contra indicated by the patient s general con t The standard surgical procedure used was bilateral ngo-oophorectomy and total hysterectomy In non al operations the uterus was not removed however Infracolic omentectomy was mainly performed only in cases with apparent or suspected omental metastases

Fertile patients with mucinous cystadenocarcinoma limited to one ovary and without tumour growth on the surface were treated with salpingo-oophorectomy only on the side involved and with a wedge resection of the remaining macroscopically healthy ovary When microscopy showed only unilateral disease no further treatment was given

Radiotherapy was started 1–3 weeks after surgery External radiation was administered to one abdominal and one dorsal field Irradiation parameters 180 kV HVL 1 mm Cu SSD 70–80 cm field size about 600 cm² Treatment was as a rule started with the dorsal beam one fraction a day with a peak absorbed dose of approximately 4 Gy (400 rad) per fraction to a total of 20 Gy (2 000 rad) Three weeks after conclusion of the first series the second series to the abdominal field was started with a daily peak absorbed dose of 3 Gy (300 rad) up to a total of 20 Gy (2 000 rad) The midabdominal absorbed dose for external therapy was usually about 12–15 Gy (1 200–1 500 rad)

Supplementary intracavitary treatment was given once or twice in most cases in connection with the external treatments A rod shaped applicator Ø 7 mm×72 mm 5 6 GBq equivalent to 150 mCi ²²⁶Ra was placed in the uterus for 6–1? hours or a flat applicator 5 mm×44 mm×44 mm 4 2 GBq equivalent to 110 mCi ²²⁶Ra was placed in the upper part of the vagina for 13–14 hours in patients having had a hysterectomy

It was not possible to use the standard surgical procedure in all of the Stage II and Stage III ovarian carcinoma patients Only an exploratory laparotomy was performed in some of them and in some cases it was not possible to remove all the demonstrable tumour If the tumour regressed in such patients or remained unchanged during 2 months observation following radiotherapy relaparotomy was performed at the Gynecological Section of the Department of Oncology except in those cases where this measure was contra indicated by the patient s general condition

The day after relaparotomy had been performed Melphalan was infused intravenously for 6–8 hours (1 mg/kg body weight to a maximum of 60 mg) Three to-four infusions were given at 4 week intervals and if by

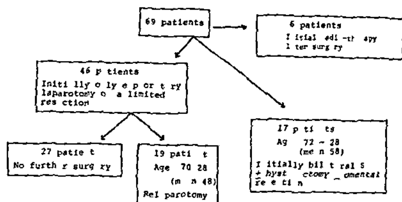


Fig 1 Treatment scheme for carcinoma Stage III

then there was any evident tumour progression no further chemotherapy was given The interval was otherwise increased to 8 weeks during the following year and to 12 weeks the second year following surgery During the ensuing years chemotherapy was given two-to four times a year

In patients who had not had a relaparotomy recurrences and/or metastases after the conclusion of radiotherapy were treated with Melphalan using the same do age described above No further chemotherapy was as a rule given when Melphalan therapy failed

The distribution of patients with Stage III ovarian carcinoma is shown in Fig 1 Nineteen patients had a relaparotomy after a limited initial surgical procedure whereas 17 patients were initially submitted to a rather extensive operation The results of therapy in these two groups will be analysed

The original histological specimens of the above mentioned 36 patients have been re evaluated The distribution of histological types among patients in the two groups is presented in Table II

RESULTS

The relaparotomy in the 19 patients was performed at a mean of 4 6 (range 4–9) months following initial

Table I *Ovarian carcinoma 1971–73*

Stage	Number of patients	Per cent of total
I A	49	22
I B	11	5
I C	1	<1
II A	11	5
II B	24	11
III	69	31
IV	24	11
Unoperated	31	14
Total	221	

surgery In 9 cases only an exploration was p ble whereas in 10 patients the adnexa or t thereof could be removed and two of t a hysterectomy In 7 cases all demonstrated t could be removed and in one case onl tumour was left

The results of therapy (NED=No Evide Disease and respectively deceased of carcinoma) are shown in Table III for pa tially given extensive surgery and for pa ing a relaparotomy after limited initial surg results are calculated from the time of operation Of 19 patients having had a rel after limited initial surgery 8 are alive whereas 11 have died from ovarian carcino 17 patients initially given extensive surg are alive NED and 12 have died from their Both of these groups of patients have the mean observation time

DISCUSSION

Laparotomy should be performed if not oth contra indicated in patients with suspected carcinoma even if presurgical staging indica the tumour may not be resectable Fine ne ration biopsy will often establish a cancer d prior to the operation and also often cl tumour (4) Cytology cannot as a rule be however for determination of the respec ation therapy and chemotherapy Some pa may not benefit from presurgical radiot chemotherapy and laparotomy should performed as soon as possible Fur tumours judged prior to surgery as not be able may well prove to be so at operation

The type of operation that should be

ble II *Distribution of histological types among tients in different treatment groups*

	19 patients relaparotomy after limited primary surgery	17 patients primarily given extensive surgery
ous papillary adeno rcinoma and cystadeno-rcinoma	9	10
icinous adenocarcinoma id cystadenocarcinoma	1	3
icinous cystadenoma of orderline malignancy	1	0
dometrioid carcinoma	1	0
ar cell adenocarcinoma	0	1
xed epithelial tumour iucinous + serous adeno rcinoma)	0	1
differentiated carcinoma	3	?
classified epithelial mours	4	0

vanced ovarian carcinoma has been the subject of ch debate Apparently no radical operation can performed when there are widespread peritoneal tastases in the pelvis and the abdomen or when re is a large fixed pelvic tumour Only a biopsy l then be possible Radiotherapy and chemo-rapy can on the other hand only be expected to duce lasting remission if at the most only mini l neoplastic tissue is left (1 2 6 7 11 13) More ensive techniques have been described by dson & Chir (1973) where an extraperitoneal bilization and extirpation of the pelvic contents re employed and even large tumours could be ically excised The tumour is however often d to the large vessels and transecting these in attempt to excise as much tumour as possible s not seem to be warranted There may be great iculties with hemostasis and the risk of massive semination of viable tumour cells is possible ich may convert the procedure into an exercise umour dissemination (7) To avoid this situa only a biopsy should be performed in cases re the tumour is apparently not radically resect e This was the case in two-thirds of the 69 Stage patients in the present series

he postoperative radiotherapy given in the sent series has been more or less the same for ients who initially only had an exploratory ration and for those who had a more extensive cedure

Relaparotomy was performed as a standard procedure in all cases where the tumour did not progress or where the condition of the patient did not worsen during radiotherapy The aim of re laparotomy was in all cases to remove remaining tumour

Relaparotomy was considered to be indicated in more than one third of the patients who had initially only had an exploration In about one half of these patients it proved to be possible to remove all or major parts of the tumour at relaparotomy

The radiation absorbed from the dose ad ministered is rather small due to tissue tolerance but in several cases has resulted in a marked reduc tion of the tumour as has also been reported from other centres (5 6 7 10) A similar effect has been reported for chemotherapy by Smith et al (8)

The further clinical course of the patients who had had relaparotomy showed that in the 8 patients in whom all or almost all demonstrable tumour had been removed no evidence of disease could be shown at the end of the follow up period 11–61 months after initial surgery This result is better than that obtained in the group of patients where all or almost all tumour was removed at the initial operation The two groups are however not strictly comparable The patients undergoing re laparotomy were younger which usually implies a better prognosis in ovarian carcinoma and fur thermore started chemotherapy immediately after the second operation whereas such therapy was not given the other patients until recurrence or metastases had appeared

The distribution of histological diagnoses also dif fered slightly in the two groups

The results may indicate that in advanced ovarian carcinoma chemotherapy should be started immediately after postoperative radiotherapy in

Table III *Treatment results for operated ovarian carcinoma Stage III*

	Initial limited surgery + relapa rotomy (19 patients)	Initial extensive surgery no relapa rotomy (17 patients)
Alive NED after	8 pats 11–61 (38) months	2 pats 38 40 months
Deceased after	11 pats 5–53 (0) months	12 pats 3–50 (?1) months

stead of waiting until the residual tumour has grown to detectable size

CONCLUSIONS

Surgery is the main therapy for ovarian carcinoma As much tumour as possible should be removed but a demand for a radical procedure should not force the surgeon to transect large tumour masses since that may result in tumour dissemination In such cases only a biopsy should be performed and postoperative radiotherapy should then be given Such therapy will often result in marked tumour reduction in size and in some patients any remaining tumour can be successfully removed at re laparotomy The present study indicates that such combined therapy may be of value The role of chemotherapy in this treatment situation has not yet been fully clarified and is the object for further investigation

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Submitted for publication Feb 24 1977

G Frick
Dept of Oncology
Gynecologic Section
University Hospital
S 221 85 Lund
Sweden

Acta Obstet Gynecol Scand 57 169–171 1978

BIPOLAR CAUTERY FOR LAPAROSCOPIC STERILIZATION

Erik Gregersen and Jens Jørgen Kjer

From the Department of Obstetrics and Gynecology Gentofte Hospital Copenhagen Denmark

tract Laparoscopic sterilization with a bipolar trode was performed in 62 patients The sterilization d in one patient and was questionable in another The tiveness was assessed by hysterosalpingography G) in 51 patients No complications due to roscopy occurred The method is considered to be antageous because of the low risk of complications effectiveness of the method seems to be acceptable

aroscopic sterilization is usually performed by ulation with a single electrode placed in a ip and with a ground plate placed on the but of the patient causing the current to pass ugh the patient as described in Fig 1 *A* How the method is associated with a certain risk of ing unplanned sites especially bowel and ab nal wall (2 14) If the contact between patient groundplate is inadequate the current be es erratic and may pass through the operator he anaesthetic equipment However intimate wledge of the instruments and routine in the ation can reduce the frequency of complica (5 6 8 10) Nevertheless despite all precau complications do occur The use of a bipolar rode (4 12 13) can also serve to reduce the plications rate on account of the short circuit 1 *B*) We have tested the method and the re are shown below

MATERIAL AND METHOD

ig the period 17 10 1975–25 2 1976 laparoscopic ization was performed in 6? unselected patients For peration Karl Storz s laparoscope and accessory ment were used Double incision technique was used incision along the lower border of the umbilicus and er a few centimetres above the symphysis)

terization was performed with the bipolar electrode 4 cm from the uterine cornu There was no transection of the fallopian tubes An Erbotom F2 was used as current source

When legal abortion was to be performed this procedure was done first

In the puerperium sterilization was performed between the 3rd and the 5th day post partum Shortly before the operation 1 ml of oxytocin was administered intravenously to obtain maximum contraction of the uterus Because of the large uterus the lower incision was placed a few centimetres below the umbilicus For the same reason the patients were not placed in the head-down position and special care was taken

Curettage was performed if the sterilization took place in the secretory phase of the endometrium in order to exclude pregnancy

The patients were advised to use contraceptives until control hysterosalpingography was performed at least 3 months after the operation

The period of observation varied between 9 and 12 months

To allow for possible change of mind a waiting time of at least 3 months from receiving the admission papers to the admission was endeavoured however the waiting time was often prolonged because of the number of admissions An endeavour was made to avoid sterilization and legal abortion simultaneously as an unwanted pregnancy can influence the decision concerning sterilization The patients were fully informed about the method and were told that the resulting tubal occlusion was considered to be irreversible

RESULTS

The age distribution of the 62 patients is shown in Table I The youngest was 25 and the oldest 43 years The mean age was 33 3

The average number of pregnancies was 3 5 (0 9 abortions and 2 6 births) Maximum was 9 pregnancies in the same patient (5 births and 4 abortions)

The operation was usually performed in less than 30 minutes The patients were without symptoms shortly afterwards and usually they were dis

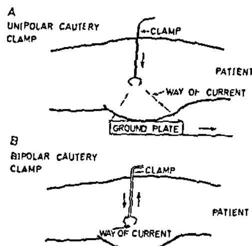


Fig 1 The two types of cautery

charged the following day so that the average hospital admission was 3 1 days Four of our patients had another simultaneous operation (3 conizations and one vaginal repair)

No immediate complications occurred In one case the uterus was accidentally perforated at curettage No bleeding was seen through the laparoscope She stayed one extra day in the department and no further problems were observed Another patient had fever (38°C) for one day without focal symptoms No antibiotic treatment was given and the cause remained obscure

Four patients were sterilized on the 3rd and 4th day of the puerperium

Legal abortion was simultaneously performed in 2 patients Both of them were 35 years old One had used various contraceptives without success resulting in 7 pregnancies The other patient had been waiting for a long time for the operation

Postoperative hysterosalpingography was performed in 51 patients (82 3%) 50 had occluded fallopian tubes In a 37 year old patient a small fistula at the site of the cauterization on the right side was revealed by HSG performed 16 weeks after the operation HSG repeated 7 months later showed a larger spillage into the peritoneum This patient was offered a new sterilization but because of lack of ability to metabolise curare she refused to undergo a further procedure As an alternative she was recommended to use conventional contraception As she had not used contraception in the interval between the hysterosalpingographies the risk of pregnancy was supposedly low

In one patient legal abortion was performed in the

Table I *Age of patients*

Age (years)	Number
<25	0
25–29	13
30–34	23
35–39	23
≥40	3
Total	6[illegible]

8th week of pregnancy 10 weeks after th[illegible] tion At the sterilization this patient had a c[illegible] performed too and thus seemed to have c[illegible] in the following cycle The patient had [illegible] contraception subsequently HSG exa[illegible] weeks later showed occluded tubes

HSG was not performed in 11 patien[illegible] failed to attend in spite of three appoi[illegible] one patient did not want HSG performed [illegible] patient HSG was impossible because of [illegible] conization and in another patient hys[illegible] was performed because of a premalig[illegible] before HSG was available At the opera[illegible] sterilization was found to be successful One [illegible] was operated on for ectopic pregnancy 11 [illegible] after the sterilization At the operation the [illegible] tube seemed to be closed but it was re[illegible] order to make the occlusion definitive [illegible] doubt She had not used the recomme[illegible] traception

No pregnancies occurred later than 3 [illegible] ter the sterilization HSG was performed [illegible] tients 10–11 weeks after the sterilization [illegible] remaining patients HSG was performed [illegible] weeks or more

Prior to HSG the patients were see[illegible] patient clinic The scars were hardly [illegible] was appreciated by the patients

DISCUSSION

The advantages of the bipolar electr[illegible] limited current flow the low voltage le[illegible] tion of uncontrolled spread of the curre[illegible] small cauterized area which may be [illegible] restoration of tubal potency is req[illegible] quently (4 12 13)

No laparoscopic complications occu[illegible] material

Double cauterization without cutting the tube . performed This was found effective by Jordan al (7) In our series one tubal fistula was found at the site of cautery This may arise with all methods sterilization There may be a risk of ectopic preg ncy (15) making resterilization advisable HSG ves rise to a risk of artificially opening the tube 4) which may have occurred in the above ntioned case For this reason it is not advisable use routine HSG as a control of the success of rilization unless a low injection pressure is used 5) A defined observation period may be used stead (9)

The efficiency of the bipolar electrode seems to the same as with the unipolar electrode (3 7) ie number of failures in laparoscopic sterilizations estimated to be 0 1–2% (11) The most common ison for failure is that the woman is already gnant at the time of the operation Therefore patients in the present series had curettage rformed if they were in the luteal phase Another ison for failure is inadequate contraceptive pre ation before the fibrosis at the cauterized sites had time to occur This seems to take about 3 onths (1 3 7) This was the reason why the pa nts were advised to use contraceptives for 3 onths or more (until the result of HSG was availa) Two patients who had not used contraception iceived during the first 3 months The preg icies could not possibly have been present at time of sterilization

The method has one significant disadvantage—it s not offer immediate sterility This drawback is inherent in unipolar sterilization

t is concluded that this method is preferable to polar electrode cautery since the efficiency is ceptable and about the same as that of the unipo- electrode and because it has several advantages

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Submitted for publication Jan 1 1977

Erik Gregersen
Jørgasvej 15
DK 7100 Vejle
Denmark

Acta Obstet Gynecol Scand 57 173–175 1978

AN ABDOMINAL APPROACH TO THE SURGICAL REPAIR OF POST HYSTERECTOMY VAGINAL INVERSION

D B Kaskarelis

From the 1st Obstetric and Gynaecological Clinic
Athens University Alexandra Maternity Hospital Greece

ıe repair of total prolapse of the vagina following ıal abdominal or vaginal hysterectomy is one of ˑ problems of gynaecology

Conservative management by use of various pes of pessary has not only given disappointing sults but even caused inflammation and ulcera on which may occasionally result in carcinoma us change Furthermore in women who continue have an active sexual life marked psychosomatic turbances may be produced It follows that the ly treatment of total prolapse of the vagina is the rgical repositioning of the vagina in its physiolog ıl position For this reason many techniques using abdominal or vaginal approach have been advo ted These techniques are technically intricate d sometimes have unpleasant complications for patients Furthermore the operations using the ginal approach cause contraction of the vagina ıding to complete apareunia

For these reasons we thought of applying a technique which will as far as possible be simple devoid of complications and will not interfere with the patient s sexual life allowing the free performance of intercourse

Following the routine preoperative preparations and under general anaesthesia the vagina is replaced in its physiological position After this the abdominal wall is opened and the intestines are packed upwards with abdominal packs

Subsequently as indicated in Fig 2 the vaginal stump is grasped by toothed forceps and three long interrupted sutures are placed in the stump using silk (Figs 3 4) The separate ends of each suture are brought one by one to the right and left of the abdominal wall piercing the peritoneum the rectus abdominis and the rectus sheath 4–5 cm above the symphysis pubis (Figs 5 6) They are left free the ends being held by Kocher s forceps This is followed by closure of the abdominal wall up to the stage where the sheath of the rectus abdominis is



F 1 Complete vaginal prolapse after total hysterectomy



Fig 2 Complete vaginal prolapse The abdominal wall has been opened The vaginal stump is grasped and drawn by toothed forceps

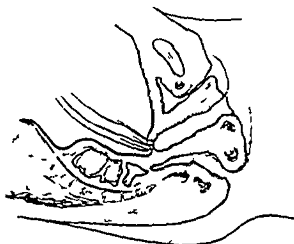


Fig 3 Three long interrupted silk sutures are placed in the stump as shown on this diagram



Fig 4 Abdominal view of the same operative stage as in Fig 3

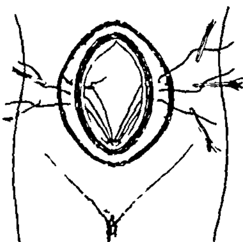


Fig 5 The ends of each suture are brought to the right and left of the abdominal incision piercing the peritoneum rectus abdominis and rectus sheath 4 to 5 cm above symphysis pubis The ends are left free being held by toothed forceps



Fig 6 The same stage on the operating table

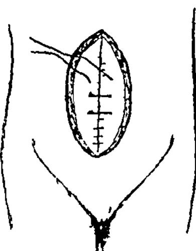


Fig 7 Traction is applied to the stump which is fixed to the abdominal wall After the incision has sutured except for the skin the forceps are rem by one and the sutures are tied with multiple kn

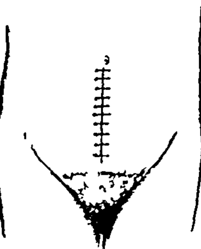


Fig 8 The skin is sutured





9 10 The post-operative results show complete ppearance of the vaginal prolapse

ured The forceps are then removed one at a and the ends of the sutures are pulled upwards are tied with multiple knots (Fig 7) The skin is n sutured (Fig 8)

during the course of the operation adhesions found connecting the vaginal stump to the ntum or intestines or if the vaginal stump has ered to the bladder or the rectum these are ld before insertion of the sutures In cases of ocele posterior colporrhaphy should be per ned

'e have performed the operation in eight cases se operated on were aged 50 to 57 years

1 all cases except in one in which we used nofilament polyamide and the suture tore ugh the tissues postoperative recovery was npletely uneventful without any bladder com ations

The patients were followed up for 1-3 years and all were found to be well and without complaints The vagina was found to be in the same location as that established during the operation (Figs 9 10) and sexual intercourse was being performed fully and without pain

These findings indicate that this surgical tech nique is simple easy safe and without any of the complications associated with the urinary bladder which one might have expected It is furthermore possible for this operation to be performed by any gynaecologist with limited surgical experience

Submitted for publication February 27 1977

D B Kaskarelis
1st Clinic of Obst and Gyn
University of Athens
Greece

Acta Obstet Gynecol Scand 57 177–178 1978

CASE REPORTS

DECREASED FETAL MOVEMENTS AND POLYHYDRAMNIOS

E Sadovsky and M Perlman

From the Department of Obstetrics and Gynecology and Neonatal Unit Hadassah University Hospital Jerusalem Israel

tract It was previously demonstrated that in high risk nancies pronounced reduction of fetal movements l cessation with audible fetal heart sounds indicates re fetal distress and impending death Immediate de ry is indicated provided the fetus is viable Three ances of cessation of fetal movements associated with hydramnios are reported the fetuses proved to have formations lethal for the newborn infant These cases polyhydramnios with diminished fetal movements ss the importance of investigating fetal morphology this condition Antenatal diagnosis of congenital malies may influence decisions about intervening in s of decreased fetal movements

re has been increasing interest recently in the ervation of fetal activity as an indicator of fetal l being and distress and a number of authors e suggested that daily recording of fetal move its (FM) may be useful in monitoring high risk nancy (1 2 3) In high risk pregnancy pronced reduction followed by cessation of FM le heart sounds are still audible has been refer to as the movement alarm signal (MAS) h may indicate severe distress and impending h (3 4) MAS may possibly serve as an indica for immediate delivery provided the fetus is le in terms of maturity On the basis of the wing case reports it is suggested that the in retation of diminished FM to cessation in hydramnios may be evaluated differently

CASE REPORTS

I D E aged ?4 years was admitted in the 36th week r first pregnancy due to abdominal pain vomiting and hea for several days On examination the uterus was l to be enlarged and the smaller fetal parts were not ble hydramnion was diagnosed The above symp- continued for a week and despite the intravenous nistration of fluids maternal ketonuria and exhaus supervened Fetal movements decreased gradually g this period and ceased for more than 1? hours ean se tion was performed and excessive amniotic was noted on opening the uterus A ? 5 kg female t was delivered with microcephaly encephalomenin gocele and respiratory distress and she died 10 min after birth At autopsy the only finding apart from the cerebral anomaly was hypoplasia of the lungs

Case 2 P S aged 24 years married to a first cousin was gravida V para III She was admitted in the thirty second week of pregnancy because of hydramnios She reported that during the present pregnancy movements were fewer than in her previous gestations and that she had felt no movements for the past week Fetal heart sounds were normal It was decided not to induce labor although the MAS indicated fetal distress Three days later after premature rupture of membranes and vaginal bleeding a 1 15 kg stillborn infant was delivered spontaneously The placenta weighed 500 g and showed signs of abruption Examination of the fetus including radiological skeletal survey established a diagnosis of achondrogenesis

Case 3 B S aged 31 years gravida III para I was admitted in the thirty sixth week for severe long standing polyhydramnios Fetal movements were within normal limits but one week later they diminished to cessation for twelve hours fetal heart tones were normal A day later the fetal heart was inaudible and a week later a macerated hydropic male fetus weighing 3 2 kg was delivered spontaneously Autopsy revealed anomalies of the alimentary tract as well as a large cystic lesion of the left adrenal gland

DISCUSSION

Polyhydramnios is associated with congenital anomalies in more than 25% of the cases and with perinatal death in about 50% (5) Anomalies vary from lethal cranial malformations such as anencephalus (as in case 1) to correctable obstructive lesions of the fetal alimentary tract (possibly represented by case 3) But a significant proportion of cases of polyhydramnios are unexplained and unassociated with fetal and neonatal mortality and morbidity Long standing diminutions of FM in hydramnion may reflect either an abnormal motility of the fetus associated with the underlying anomaly or a dampening of FM by the increased volume of amniotic fluid Disappearance of FM preceded fetal death in cases 2 and 3 analogous to the similar natural history of diminishing FM in the fetus of high risk pregnancies (4)

The above observations indicate that one should be cautious when evaluating diminished FM in pregnancy complicated by hydramnios The coexistence of diminished FM and polyhydramnios is highly suggestive of fetal malformation as shown by full investigation of fetal morphology as well as evaluation of the feto-placental unit In this situation the performance of fetal radiography ultrasonography and/or fetography and examination of *α fetoprotein in the amniotic fluid may be helpful* in deciding about pregnancy intervention

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Submitted for publicati n April 30 1977

E Sadovsky
Department of Obstetrics and Gynecology
Hadassah University Hospital
Ein Karem
Jerusalem
Israel

Acta Obstet Gynecol Scand 57 179–181 1978

ACUTE FATTY LIVER OF PREGNANCY WITH DISSEMINATED INTRAVASCULAR COAGULATION

Per Moldin and Olle Johansson

From the Department of Obstetrics and Gynecology Central Hospital Boras Sweden

tract A patient with acute fatty liver of pregnancy ociated with disseminated intravascular coagulation C) is reported The case lends support to the hypot is that DIC may be of pathophysiologic significance in disorder Treatment principles are discussed and the ortance of prompt Caesarean section as early as possi after the onset of symptoms is emphasized

seminated intravascular coagulation (DIC) has n reported associated with complications of gnancy for instance in abruptio placentae tox ia missed abortion saline abortion amniotic d embolism post partum haemorrhage and sep abortion Recently an association between DIC acute fatty liver of pregnancy has been erved (3 7) It is normal in pregnancy for a nber of coagulation factor levels to increase tors I II VII VIII IX and X) and the fibrino- activity of the blood is reduced (1 9 11) edt et al (14) have demonstrated decreased inolytic activity in vein walls during pregnancy se changes it is suggested contribute to the esis of DIC during pregnancy There is a diver ce of opinions concerning the treatment of DIC regnancy Despite different regimes high mor y rates are reported The intention of the fol ing report is to document a case with acute fatty r of pregnancy with evidence of DIC during the d trimester

CASE REPORT

-year-old primipara whose last menstrual period was 1975 had previously had a cholecystectomy at the age urteen During the 8th week of gestation vomiting and einuria occurred but these symptoms soon subsided serum creatinine remained normal Oedema appeared ng the 32nd week and Chlorthiazid (Chlotride®) 0 5 g was prescribed In spite of this therapy her weight increased by 5 kg during the following 11 days During the 36th week she was admitted to hospital after 4 days of nausea vomiting abdominal pain and slight generalized itching She had lost 3 5 kg in weight during these 4 days On admission to the hospital slight oedema was evident in the face and hands The initial blood pressure was 170/80 mmHg temperature was normal and foetal heart rate was 140/min Electrolytes were normal on the following morn ing except for a raised serum creatinine (?64 μmol/l) Serum creatinine increased during the following 2 days in spite of intravenous fluid therapy and a urinary output of 900–1 650 ml per day (Table I) Vomiting continued and on the second day she became somnolent and jaundiced with a serum total bilirubin of 88 μmol/l (Table I) Foetal heart rate remained normal Because of her deteriorating condi tion the pregnancy was successfully terminated by Caesarean section under general anaesthesia Grossly meconium stained amniotic fluid was observed during the operation but bleeding was strikingly small 500 ml dex tran (Macrodex®) was given as a routine during the opera tion A few hours after the Caesarean section the presence of DIC with secondary fibrinolysis was suggested by thrombocytopenia prolonged activated partial thrombo- plastin time (APTT) fibrinogen/fibrin degradation pro- ducts more than 40 mg/l (Wellcome Thrombo-Wellcotest) hypofibrinogenaemia and signs of fibrinolysis in the blood (Table II) Treatment was initiated with dextran fresh blood fresh plasma and vitamin K No heparin was given after consultation with an expert on coagulation defects Clinical improvement commenced 24 hours after delivery with declining somnolence and oedema Urinary output was high and urinary osmolarity low (170 mmol/l) The eyegrounds were normal During the 2 days following the operation there was a transitory reduction of arterial ox ygen tension (Table I) Pulmonary X ray revealed a dis crete central patchy opacity in the lungs Serum total bilirubin reached a maximum of 213 μmol/l on the fourth day after delivery (Table I) Au antigen was negative No bleeding tendency was observed postoperatively The placenta was normal on histological examination The pa tient was discharged home 2 weeks after delivery At a later assessment she was clinically healthy and had normal biochemical values

The baby s Apgar score was 10 one and five minutes after birth birth weight 2830 g Because of respiratory

Table I

	Hospital day									
	1	2	3	4			5	6	7	9
			Caesarean section							
S Creatinine (<115 μmol/l)	264	380	400	410	90		100	?10		[illegible]
S Protein (60–80 g/l)	62	58	45	5?	59		60	55		
S Sodium (138–148 mmol/l)	140	134	130		141		140	147		
S Bilirubin (3 0–20 μmol/l)		88	85		136		168	?13	180	[illegible]
S ALP (1 3–5 0 μkat/l)		24	?0				16	13	13	
S ASAT (<0 70 μkat/l)		3 4	2 6							
S ALAT (<0 70 μkat/l)		5 5	3 9							
aB pO_2 (10–13 kPa)			15 0	9 9	8 3	10 5	10 7			
Urinary output (ml/day)	900	1 650	4 550		5 ?00		1 575	1 950	2 150	

distress and tachypnoea treatment with continuous positive airway pressure was instituted for two days Antibiotic therapy was given The child had a normal platelet count and was discharged from hospital 18 days after birth in good condition

DISCUSSION

This patient presented clinical symptoms and laboratory abnormalities consistent with DIC with secondary fibrinolysis Thus there were symptoms and signs of functional disturbance relating to a number of different organs liver insufficiency with jaundice renal insufficiency with elevated level of serum creatinine cerebral disturbance with somnolence abdominal pain and vomiting placental insufficiency with meconium stained amniotic fluid and pulmonary insufficiency with reduced arterial oxygen tension and an abnormal X ray picture Biochemically thrombocytopenia hypofibrinogenemia fibrinolysis fibrin[illegible] degradation products in serum and a prolo[illegible] were documented A reduced level of [illegible] in serum indicated some haemolysis which [illegible] caused by intravascular coagulation (9)

The similarity of the presenting sympt[illegible] plex to that which is classically described f[illegible] fatty liver of pregnancy was striking Th[illegible] drome was first reported by Sheehan [illegible] obstetric acute yellow atrophy (1?) [illegible] is still unknown but the syndrome only o[illegible] pregnancy A typical and specific liver [illegible] seen The disease usually begins in the [illegible] ter with a sudden onset of nausea and [illegible] epigastric pain progressive jaundice [illegible] and sometimes haematemesis Acute renal [illegible] with oliguria is also part of this synd[illegible] prognostic outlook is grave and mat[illegible] perinatal mortality rates of 85% are repor[illegible]

Table II

	Hospital day												
	1	2	3		4				5	6	7	8	9
			Caesarean section										
B Hemoglobin (120–160 g/l)	162	14?	128		140	1?1			118	119	134	1?	
Leukocytes (4–9×10⁹/l)				11 1		1? ?			11 5				
Platelet count (100–400×10⁹/l)			5	33	105	98	68	66	68	86	?0	1	
P APTT (<45 s)			80	85	70	75			8?		9	4	6
P TT (70–130%)			?7	17	15	11	19		16	41	?0	9	
S FDP (<10 mg/l)				>40			>40						
B Fibrinogen			sign	reduced									
Fibrinolysis			sign	increased									

B Fibrinogen and test for fibrinolysis according to Sharp & Eagleton (J Clin Path 16 351 19?3)

ently an association between DIC and acute y liver of pregnancy has been observed (3 7)

patient also presented clinical symptoms and oratory abnormalities compatible with DIC This ervation lends support to the hypothesis that avascular coagulation may be of patho-siological importance for the development of ical symptoms and signs in acute fatty liver of gnancy

herapeutically Haemmerli (6) points out that the y chance for both mother and child is Caesarean tion as early as possible after the onset of symp is of acute fatty liver In accordance with these / observations of an association between DIC acute fatty liver of pregnancy this therapy still ns to be the most appropriate Most authors e that in cases with DIC the underlying disorder be treated primarily (8 9) DIC is a sign rather a disease and is treated by removing the cause In acute fatty liver of pregnancy it is the preg cy itself which is to be considered as the se Interruption of pregnancy as soon as possi after the onset of symptoms therefore seems to he therapy of choice In the described case this tment was successful for both mother and child

eparin treatment has been suggested (3 7 10) considering the mainly prophylactic effect of arin it has to be given early in the course of the ase to have a beneficial effect There is also an ous risk of serious bleeding with heparin inistration especially after surgery This pa presented manifest abnormal function as-ated with a number of organs before DIC was d As there was also a risk of postoperative ding heparin treatment was ruled out after con ition with an expert in coagulation defects operative treatment was given with dextran blood fresh plasma and vitamin K in order to further formation of microthrombi and to com ate for the deficit of platelets fibrinogen and r coagulation factors

ACKNOWLEDGEMENT

We wish to thank Prof Inga Marie Nilsson Coagulation Laboratory Allmanna Sjukhuset Malmo for valuable guidance and criticism

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Submitted for publication Jan 31 1977

Olle Johansson
Department of Obstetrics and Gynecology
Centrallasarettet
S-501 15 Borås
Sweden

Acta Obstet Gynecol Scand 57 183–185 1978

DELIVERY COMPLICATED BY MYASTHENIA GRAVIS AND EPILEPSY

U Hansson L Irestedt and P J Moberg

From the Departments of Obstetrics and Gynecology and Anaesthesiology Karolinska Sjukhuset Stockholm Sweden

ract The literature on the possible risk of myasthenia is complicating pregnancy and delivery is sparse and y contradictory but some of the reports on the ber of perinatal and neonatal deaths are alarming psy in pregnancy implies an approximately twofold of intervention in connection with labour A pregnant nt with myasthenia gravis and epilepsy has recently delivered The case is reported and the considera with regard to suitable anaesthesia and the two dis s are discussed

re are few published reports of Myasthenia vis (MG) associated with pregnancy and deliv (10 11 14 15) and of Epilepsy (Ep) as a poten risk in pregnancy (1 8) As far as can be de ined there is no report of a combination of e illnesses complicating pregnancy–delivery igh one has described complications of the perium (13) A pregnant patient with MG and has recently been treated at the department of tetrics and Gynecology Karolinska Sjukhuset kholm and a report is given

CASE REPORT

patient aged 35 was primigravid She had had Ep pathic grand mal) since the age of 15 years and MG 31 years of age Her Ep was well controlled with ytoin (Diphydan®) 0 1 gram four times daily and her was controlled by pyridostigmin bromide (Mestinon®) ig three times daily as a previous thymectomy had ided no relief During the pregnancy she was given ks regularly at the hospital including control of her m phenytoin The pregnancy progressed normally and was delivered in the 39th week by caesarean section ormed under general anaesthesia and managed in the wing way

o premedication was given Preoperatively she was ed in left lateral position and was hydrated by means n intravenous infusion of 500 ml acetated Ringers tion ECG was monitored continuously Prior to in duction of general anaesthesia 95 ml prilocaine (Citanest® 2 5 mg/ml) was infiltrated subcutaneously below the umbilicus on both sides of the midline The patient also received 0 5 mg atropine i v General anaesthesia was induced by spontaneous inhalation of nitrous oxide in oxygen (60–70%) and halothane (Fluothane®) was added in an increasing concentration to a maximum of 3% im mediately before intubation which was then easily performed without the aid of any muscle relaxant Halothane administration was then stopped and methoxyflu rane (Penthrane® 0 2–0 6%) was added to the nitrous oxide–oxygen mixture After intubation the patient was moderately hyperventilated by manual positive pressure ventilation The induction–delivery interval was 10 min utes The course of the anaesthesia was uneventful and after completion of the operation the patient quickly re covered consciousness regained adequate spontaneous ventilation and was extubated She was observed in the postoperative ward the following 12 hours without show ing any signs of complications such as muscular weakness or impaired ventilation No medical postoperative anal getics were required The child was in good condition at delivery with an Apgar score of 8 at one minute and 10 at 5 minutes and was observed in the neonatal department for 3 days without any signs of neonatal myasthenia ap pearing The postoperative recovery was uneventful and 6 weeks after delivery there had been no exacerbation of the MG or Ep

DISCUSSION

Influence of MG

Because of the sparse and to some extent con troversial literature relating to MG and pregnan cy–delivery (4 7) it is difficult to establish a clear cut pattern of the complications particularly those due to MG A woman with a known and well controlled MG can experience a normal pregnancy and a vaginal delivery perhaps instrumentally aided (4 10 14) Caesarian section should be used according to usual obstetric indications (14) Miller

et al (11) point out the risk of (*a*) prolonged labour and (*b*) a potential maternal and fetal danger of MG in 5 patients with 7 pregnancies there was one intrapartum fetal death and one postpartum maternal death Some authors however have said that labour may be shorter than expected because of relaxation of voluntary muscles (14) McNall & Jafarnia (10) reported 5 patients who had a total of 9 pregnancies ending in one stillbirth and 7 live born babies of whom 2 died in the immediate neonatal period Hay (7) has published a very thorough review of the literature relating to MG and pregnancy and in addition has reported on further 6 patients concluding that the combination must be regarded as a serious threat to life Out of 9 pregnancies there were two maternal and three perinatal deaths These reports thus support the view expressed by Miller et al (11) that MG associated with pregnancy is a potential danger To obtain pain relief during labour the use of a regional block is advisable although small doses of local anaesthetics are recommended (2 6) Sedatives and narcotics should be used with care due to the potential risk of increasing muscular weakness (6 7 10) If emergency operations such as forceps delivery or caesarian section have to be carried out a regional block can serve the purpose but might be too time consuming In such cases general anaesthesia must be chosen which is usually well tolerated by these patients but muscle relaxants should be avoided as far as possible (2 6 12) General anaesthesia can then be induced by an inhalation anaesthetic as these patients are usually easily intubated in a light plane of [illegible] (2) Induction by inhalation is slow however compared with intravenous induction combined with muscle relaxants A planned caesarian section is thus obviously preferable to an acute one By combining inhalation anaesthesia with infiltration of a local anaesthetic agent in the operating field the plane of anaesthesia can be kept superficial in order to avoid postoperative respiratory depression

Influence of Ep

In a study of 371 pregnancies in women with Ep Bjerkedahl et al (1) showed that complications during labour occurred with a significantly greater frequency than in non-epileptic women 19 4% vis à vis 9 6% in controls Intervention during labour was also significantly more frequent in patients with epilepsy

Influence of MG and Ep

In the present case the risk of com[illegible] labour was more than double because of [illegible] and the risk to the infant due to the MG was [illegible] Prior to labour it was necessary to d[illegible] methods would be suitable for analges[illegible]thesia in the event of vacuum or forceps [illegible]tion or caesarian section becoming ne[illegible] The combination of MG and Ep grea[illegible] the choice of suitable anaesthesia The[illegible] contra indication to employing a regional [illegible] if vaginal delivery is planned but in the case [illegible] acute complication general anaesthesia [illegible] method of choice because of reasons [illegible] above Furthermore because of their [illegible] convulsive effect local anaesthetic drugs [illegible] used in restricted amounts in patients with [illegible] When considering a planned caesarian sect[illegible] eral anaesthesia seems to be the choice [illegible] and hyperventilation could easily occur d[illegible] epidural block or a subarachnoid block and [illegible] increase the risk of a convulsive episode The[illegible] large doses of local anaesthetics migh[illegible] neuromuscular transmission thereby const[illegible] relative contra indication to epidural b[illegible] The method of general anaesthesia used in [illegible] deserves some discussion Halothane is an e[illegible]lent agent for induction but its action on [illegible] contractility is well known (3) In order [illegible] uterine inertia the anaesthesia was contin[illegible] methoxyflurane in a low dose immedia[illegible] intubation The new inhalation anaesth[illegible]flurane (Efrane®) might have been consider[illegible] sole inhalation anaesthetic for the whole [illegible] but it has been shown that this drug can [illegible] cerebral epileptiform activity and its use in a [illegible] with Ep could hardly be recommended [illegible]thoxyflurane because of its slow onset of [illegible] not useful for the induction of anaesthesia [illegible]fers good analgesia and muscle relaxat[illegible] factor is of importance where it is advisab[illegible] muscle relaxants Methoxyflurane becaus[illegible] dose related nephrotoxic effect (9) is [illegible] often used as an inhalation analges[illegible] anaesthetic but the dose administered [illegible] was well below the toxic dose As [illegible] necessitating immediate intervention [illegible] asphyxia would have been associated w[illegible] ficulties a planned caesarian section under [illegible] anaesthesia was considered to be the [illegible] ing a maximum of security to both mother an[illegible]

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Submitted for publication Febr 27 1977

P J Moberg
Department of Obstetrics and Gynecology
Karolinska sjukhuset
S-104 01 Stockholm
Sweden

Acta Obstet Gynecol Scand 57 187–188 1978

RUPTURE OF THE SPLEEN DURING DELIVERY

Susanne Christau and Joachim G Klebe

From the Department of Obstetrics and Gynecology Rigshospitalet University of Copenhagen Denmark

bstract A case of traumatic rupture of a normal spleen a complicated delivery is presented The etiology of lenic rupture and therapeutic aspects of this unusual currence are discussed It is pointed out that a violent pression of the fetus might be dangerous for the mother

ases of rupture of the splenic artery the spleen or ore usually of an aneurysm of the splenic artery association with child birth are very rare (1 15 17) Saxtorph in 1803 first reported a case of ptured spleen during pregnancy (12)

The etiology of rupture of the spleen has been nerally listed as being spontaneous due to tox nia or by trauma The following case is presented it of interest primarily because of its unusual oc irrence as one of the first traumatic ruptures in lation to a complicated delivery and because successful treatment adds a further maternal rvivor in a condition which has always carried a avy mortality

CASE HISTORY

migravida aged 24 The pregnancy was uncomplicated art from 2 weeks past term Labour began spontane sly 10 hours before she was admitted to a private clinic 1 the second stage 3 hours before In the clinic delivery h vacuo-extractor and forceps was attempted but with t success and the patient was transferred to our de rtment where the physical examination revealed the rus to be soft and term sized but the left and right pogastric areas were tender to palpation A caesarean tion was performed and she was delivered of a 4 580 g althy infant Apgar score 7 after 1 min and 10 after 5 n

The recovery was uneventful until the 6th postoperative y On the afternoon after straining at the stool she ldenly collapsed The pulse was increased and the od pressure were 50/40 mmHg Immediate attention s given to resuscitation Oxygen was administered by sk and transfusion commenced with plasma-expander emaccel®) The provisional diagnoses were made of g embolism or hypovolaemic shock The whole abdo- n seemed tender there was a slight dyspnoea The G did not show any sign of lung embolism The pa tient s condition became worse and she was transferred to the emergency department There the condition was complicated by cardiac arrest

Laboratory studies disclosed the following values Haemoglobin 2 0 mmol/l base excess 30 mEq/l standard bicarbonate 10 5 mmol/l

The patient was oxygenated through an endotracheal tube and external heart massage was performed The abdomen seemed then to be enlarged both flanks being dull to percussion After a blood transfusion of 4 units unmatched blood and intravenous administration of 1 litre of plasma expander and 1 5 litres saline her general condition improved sufficiently that a laparotomy could be performed The abdomen was opened by the caesarean section incision The peritoneal cavity was found to con tain fresh blood and clots The uterus and tubes were found to be normal On extending the incision up to the left curvature the blood was squirting from the region near the hilus of the spleen but the enormous quantity of free blood made examination difficult the splenic vessels were clamped and splenectomy was performed A 4 cm and a 1 5 cm laceration were noted on one pool of the surface of the spleen

Besides the haematoma around the spleen some or ganized haematomas on the oment at the curvatura major at the stomach were found The patient received 24 units blood 3 units plasma-expander and a few litres of saline

At the end of the operation the patient s condition had improved considerably She made a remarkable unevent ful recovery and was released on the 13th postoperative day

The spleen measured 4×7×12 cm The pathological report revealed no abnomalities in the spleen other than the lacerations

DISCUSSION

Rupture of the splenic vessels or the spleen is a very rare complication of pregnancy and is as a rule rapidly fatal the patient dying usually before oper ation can be performed The mortality is high only 17 survivors of 61 cases of massive abdominal bleeding have been reported (4) Trauma is one of the most common causes of rupture of the spleen in non pregnant persons The trauma may be external in the form of penetrating or non penetrating injury (16) The trauma may also be internal with such

causes as vomiting sneezing bending coitus straining at the stool being implicated (2)

Rupture of the spleen in pregnancy is reported in 76 cases (6 12 13) It is interesting to note that in the large proportion of the published cases the *bleeding is biphasic usually within hours of the* trauma In this patient the history spread over 6 days In our case the traumatic attempt of the delivery together with the increased abdominal pressure and the elevated central venous pressure (3) due to the manual expression of the fetus before the admission may be responsible for the lesions of the spleen The trauma at the failed vaginal delivery caused lacerations of the splenic parenchyma with or without rupture of the splenic capsule resulting in initial bleeding which is tamponated by blood clots The delayed hemorrhage or biphasic rupture occurred by rejecting the blood clots or by secondary rupture of the capsule after straining at the stool

Violent expression of the fetus therefore not only can reduce the intervillous blood flow but might also result in a dangerous condition for the mother

Splenectomy is a treatment of choice for a ruptured spleen along with liberal blood transfusion

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Submitted for publication Jan 24 1977

Joachim G Klebe
Kommunehospitalet
Dept of Obstetrics and Gynecology
8000 Århus C
Denmark

Acta Obstet Gynecol Scand 57 189–190 1978

MASSIVE ENLARGEMENT OF OCCLUDED TUBES AFTER POSTMENOPAUSAL TREATMENT WITH NATURAL ESTROGENS

Mats Hammar and Ulf Larsson Cohn

From the Department of Obstetrics and Gynecology University of Linkoping Linkoping Sweden

e here report a probable side-effect of post enopausal estrogen replacement that to the best our knowledge has not been described pre ously

CASE HISTORY

e patient was a primipara having had a normal delivery the age of 3? She had no history of pelvic inflammatory disease and the menopause had occurred by the age of 43 Four years later bilaterally occluded tubes were diagnosed at laparoscopy One of the tubes was of normal size while the other was somewhat enlarged The latter was emptied of 30 ml of clear fluid after which it totally collapsed

When the patient was 56 years old she had still marked postmenopausal vasomotor symptoms Pelvic examination showed no abnormalities and she was prescribed a combination of micronized oestradiol 4 mg+oestriol 2 mg to be taken cyclically with every 7th week free of medication

All symptoms disappeared promptly and when she was examined 7 months later no pelvic abnormalities were noted Eleven months later she was still symptom free but pelvic examination performed by the same gynaecologist as previously revealed a cystic mass

At laparoscopy followed by laparotomy greatly enlarged hydrosalpinges were found (Fig 1) They were excised and the postoperative course was uneventful The tubes were 15 cm long with a maximal width of 5 cm Both were filled with a clear fluid containing a few epithelial cells and some lymphocytes The walls of the tubes were very thin and covered with a normal single layer epithelium



? 1 Photograph showing the enlarged tubes in situ

DISCUSSION

During oestrogen administration to oophorectomized rabbits the tubal epithelium regains its secretory activity rapidly (2) and the number of regenerated secretory cells depends upon the dose administered (3) Clewe & Mastroianni (1) have reported that after castration the oviductal secretion of the rabbit fell rapidly but was restored after treatment with oestradiol

In the Rhesus monkey the maximum production of tubal fluid usually occurs within the day of maximal vaginal cornification and it was considered likely that the secretion was induced by oestrogens (5) In the human female the oviductal epithelium shows its maximum secretory activity during the

follicular phase of the menstrual cycle (4) It would thus seem in the human female that endogenous oestrogen production stimulates tubal secretory activity

It can therefore be suspected that in the case presented the fairly high doses of the two natural oestrogens estradiol and estriol stimulated the production of the relatively large amounts of fluid which filled the occluded tubes It would be interesting to know if equipotent doses of synthetic oestrogens could have a similar effect

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Submitted for publication March 6 1977

Mats Hammar
Dept of Obstetrics and Gynecology
University Hospital
S 581 85 Linkoping
Sweden

LETTER TO THE EDITOR

ear Sir

- recent letter to the Editor (Acta Obstet Gynecol Scand 55 469–470 1976) by Drs Belfrage and Raabe uses certain questions concerning the use of ɔidural anesthesia (e a) in obstetrics Since the tual problems may be approached differently we elcome this opportunity to discuss some main ɔints which may be of general interest among obetricians

Drs Belfrage and Raabe emphasize that in their cperience nearly every second primiparae has to delivered instrumentally in order to terminate e second stage of labour within 1 hour We have iown that it is possible to keep the frequency of strumental deliveries almost at the normal level ithout exceeding our limit of 1 hour for the second age (1)

Drs Belfrage and Raabe correctly assume that we ive a high frequency of episiotomies in fact 90 % primiparae This figure has been constant for ars and has not been influenced by the introduc ɔn of e a Fundal pressure has been applied in rtain cases but of course is not a routine proce ıre Fetal/neonatal welfare was evidenced by rdiotocography and high Apgar scores The lat finding has been supported by the work of atouskova et al (2)

Instrumental delivery in Scandinavia usually cuum extraction cannot be regarded as comtely innocent for the fetus In addition to the own risks of vacuum extraction we would like draw attention to the fact that severe retinal morrhage is five times more frequent in neonates livered by vacuum extraction as compared to ceps or spontaneous delivery (3) We therefore untain our opinion that it is of some importance keep the rate of instrumental deliveries at a low el

Concerning the duration of bupivacaine there is disagreement between Drs Belfrage and Raabe and ourselves However the number of doses given during labour will differ with the various routines for administering local analgesics

We do consider the occurrence of meconium stained amniotic fluid during labour and/or early cardiotocographic signs of intrauterine distress to be an indication for e a As stated by Bonica (4) this makes immediate intervention possible without using general anesthesia Moreover in our experience elimination of maternal stress is frequently beneficial for the fetal condition

The fact that only 4 of our 19 cases of intrauterine distress were delivered by caesarean section forceps or vacuum supports this assumption The 1 min Apgar scores were 9–10 in 15 cases and 6–8 in the remaining 4 cases

Jan Martin Maltau and *Harald T Andersen*
Department of Obstetrics and Gynecology
Rikshospitalet
Oslo Norway

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Submitted for publication May 9 1977

J M Maltau
Dept of Obstetrics and Gynecology
Rikshospitalet
Oslo
Norway

Acta Obstet Gynecol Scand 57 192 1978

ANNOUNCEMENTS

An *International Symposium on Cryptorchidism* will be held in Stresa Italy between June 8–11 1978 Further information can be obtained from Organizing Secretariat Serono Symposia Via Primaticcio 158 20127 Milano Italy

During the 6th European Congress of Perinatal Medicine held in Vienna Austria from August 30 to September 1 1978 the *Maternitee Pri e* of the European Society for Perinatal Medicine will be awarded for outstanding experimental clinical and organizational achievements in the field of Perinatal Medicine Persons who feel competent are kindly requested to nominate candidates not later than January 31 1978 to the President s address Prof Dr O Thalhammer Univ Kinderklinik Währinger Gurtel 74 A 1090 Wien Austria

First Congress of the International Society for the Study of Hypertension in Pregnancy 27–29 September 1978 in Dublin Ireland Enquiries to Prof John Bon.z Ch- man 1st Congress Imax I M A House 10 Fa... Place Dublin 2

The European Congress of Obstetric Anaesthesia and Analgesia is to be held at the National Exhibition Cen... Birmingham England in September 1979 The pro- gramme of the Congress is designed to be of interest ... anaesthetists midwives obstetricia...
The Congress will last for four days and
of the topics to be discussed will be

Pain relief during labour identification of and sup... tive therapy for the foetus at risk anaesthesia for ope... tive delivery neonatal resuscitation intensive care of the seriously ill neonate and intensive care of the seri... ill parturient

There will also be a full calender of Social Events ... day for delegates non participating companions

Acta Obstet Gynecol Scand 57 193–201 1978

AN ELECTROIMMUNO ASSAY OF THE PREGNANCY SPECIFIC β_1 GLYCOPROTEIN (SP_1) IN NORMAL AND PATHOLOGICAL PREGNANCIES AND ITS CLINICAL VALUE COMPARED TO HUMAN CHORIONIC SOMATO MAMMOTROPIN (HCS)

S Sørensen

From the Department of Clinical Chemistry and the Department of Obstetrics and Gynaecology Frederiksberg Hospital Copenhagen Denmark

Abstract A 95% reference interval for the pregnancy specific β -glycoprotein (SP) was established on the basis of 799 samples from 254 normal pregnant women by electroimmuno-assay (rocket immunoelectrophoresis) A positive correlation was found between SP and the human chorionic somato-mammotropin (HCS) The SP concentration in maternal blood was halved about 30 hours after separation of the placenta at delivery Thus emergency analyses would be of little value in detecting acute placentae failure 172 determinations of SP in maternal sera were carried out on 56 pregnant women with various types of pathological pregnancies To assess the clinical value of SP a comparison with HCS (HPL) was made It was concluded that SP could possibly be a valuable parameter for monitoring and discovering pathological pregnancies Larger investigations however must be performed to decide whether SP determinations will provide more extensive information than other laboratory analyses presently used

During human pregnancy the concentration of many of the normal serum proteins are changed Increased amounts of α_1 antitrypsin α_1 easily precipitable glycoprotein Gc globulin transferrin and ceruloplasmin have been reported (5 11) Other proteins appear in the blood only during pregnancy Bohn in 1972 isolated the pregnancy specific β_1 glycoprotein (SP_1) from the human placenta and presumably it is synthesized there (2) SP_1 has also been identified by Lin et al to be one of three pregnancy associated plasma proteins (PAPP C) (10) In an earlier investigation Bohn detected SP and three other pregnancy proteins in sera of pregnant women He used the Ouchterlony gel diffusion technique with antisera obtained from rabbits immunized by injection of protein fractions from human placentas (1) Another pregnancy specific protein was identified as the human placental lactogen (HPL) hormone also called human chorionic somato-mammotropin (HCS) The remaining two proteins SP_2 (identical with the steroid binding β globulin) and SP_3 (identical with the α_2 AP glycoprotein) are not specific for pregnancy These two proteins can be detected in low concentrations in sera from normal women and men and in increased levels in patients suffering from various malignant and non malignant diseases in women using hormonal contraceptives and in men treated therapeutically with estrogens

SP_1 has a β_1-electrophoretic mobility and contains 28 1% carbohydrate (2) On the basis of electrophoresis in a sodium dodecylsulfate containing polyacrylamide gel the molecular weight has been determined to be 90 000±5 000 (3) The biological function of SP_1 is unknown but SP_1 appears to have an affinity for estriol 17 β estradiol and cortisol (3)

The increasing production of SP_1 in placenta during pregnancy may provide a possibly useful placental parameter The purpose of this study has been to establish a reference range and subsequently to assess the clinical application of SP_1 determinations carried out on serum samples from women with pathological pregnancies In the groups where SP estimations appeared to be of clinical value comparisons were made with the results of HCS analyses on the same samples since HCS is also produced in the placenta

MATERIALS AND METHODS

Subjects

The study included 315 pregnant women … nearly all were admitted to the Department o… …al

Table I *The distribution of pregnant women (including age and parity) and samples according to di*

Diagnosis	No of pregnant women	No of samples	Age (years) ≤14	15–19	20–24	25–29	30–34	≥
Normal pregnancies	215	260		14	76	91	30	4
Induced abortion	39	39	1	1	8	18	8	1
Serial determinations in normal pregnancies	5	57						
Abruptio placenta	2	2			1	1		
Placenta previa	1	2				1		
Mild pre-eclampsia	9	31		1	3	4	1	
Severe pre eclampsia	3	15			2	1		
Chron hypertensive disease	3	12			1	1		1
Neonatal asphyxia	7	17		1	3	1	1	1
Prematurity	12	36		1	5	3	3	
Fetal death	11	?6			2	5	3	1
Hydatidiform mole	3	5			3			
Twin pregnancy	5	26			5			
Total	315	528						

of 528 estimations of the pregnancy specific β_1 glycoprotein were made (Table I) To establish the reference interval 260 serum samples from 215 pregnancies between the 1?th and the 40th weeks of pregnancy were investigated Results were included only for normal pregnancies for which the first day of the last menstrual period was known and which resulted in the delivery of a healthy infant with a birthweight >2500 ± 10 days from the estimated term Only cases in which the placenta was morphologically normal were included The reference material was supplemented with 39 results from 39 pregnant women in whom induced abortions were performed To provide an assessment of the course of development of SP_1 concentration during the normal pregnancy samples were drawn from five pregnant women at regular intervals during the pregnancy The results were not used in determining the reference range

Pathological pregnancies were divided into various ...ic groups (Table I) The definitions used for ...on and preeclampsia were those recommended ...the American College of Obstetricians and Gynaecologists Committee on Terminology (6) The criterion for neonatal asphyxia was an Apgar score of ≤5 one minute after delivery If the birthweight was ≤2500 g the infant was regarded as premature (including true premature born infants genetically small full term infants and full term infants with intrauterine growth retardation)

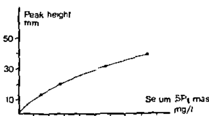


Fig 1 A standard curve for SP_1 electroimmuno assay Laboratory standard diluted to 84 56 28 and 15 mg/l

Methods

Blood sampling The samples were taken without anticoagulant and without special regard for stasis or precise time of sampling When coagulation was complete the samples were centrifuged and the serum stored at −15 C until analyzed

Antigen standard A serum pool from pregnant women in the last trimester was collected in small portions stored at −15 C and used as an SP_1 standard The pool was compared to a standard kindly supplied by Behringwerke AG Marburg Lahn K No 1093 containing 330 mg/l For 20 determinations the mean value was 168 mg/l the SD was 4 6 mg/l and the coefficient of variation was 2 7%

Antibody Rabbit immunoglobulin against SP_1 K No ?416 was from Behringwerke Marburg Lahn

Assay buffer 0 0?4 M sodium barbital buffer pH 8.6

Crossed immuneoelectrophoresis was carried out as described by Weeke (15) The standard was diluted 1+1 and ... was 1% (v/v) 10 µl applied The antibody concentration ...

Electroimmuno assay (rocket immunoelectrophoresis) SP_1 was determined as described by Laurell (9) and Weeke (14) Glass plates (205×110×1 mm) and a 1 mm thick U shaped frame were used To 1% (w/v) agarose (L'Industrie biologique Française) cooled to 60°C antibody was added to a final concentration of 1 25% (v/v) The solution was then poured into the mould After gelation the non coated plate and the frame were removed and the wells punched out (diameter=2 5 mm) The standard was diluted 1+1 1+2 1+5 and 1+10 with assay buffer (corresponding to 84 56 28 and 15 mg/l) The samples were diluted 1+3 Only a few had to be used in 1+7 dilution Samples from the eighth tenth weeks were used undiluted 5 µl of standards and samples were applied with the current switched on 2–? 5 V/cm Double determinations of

r	Para II	Para III	Para ≥IV
	64	12	6
	1		
	1		
	2	1	
	?		
	?		
	4	1	
		1	1
	1		

amples and single determination of the standard dilutions vere made The electrophoresis was interrupted after 8–70 hours and the plate was covered with a wet filter aper and dried in hot air Subsequently the plate was tained with Coomassie brilliant blue followed by de taining and drying After electrophoresis of the plates with amples from the eighth–tenth weeks were placed for 30 *nin in a 0 15 mol/l NaCl solution followed by 30 min in* estilled water This procedure was necessary to prevent on precipitated proteins from extending the immuno recipitates and making reading difficult A standard urve for the plate in question was prepared with the SP oncentration as abscissa and the peak height as ordinate In illustration is given in Fig 1 After the reading the SP$_1$ oncentration in the sample was calculated by multiplying he results by the dilution factor The most sharply in lected part of the curve corresponding to small SP$_1$ val ies was verified both for the standard from Behringwerke nd for our own standard

The *HCS estimations* were carried out routinely by a adioimmunoassay (8)

RESULTS

Methodological results

The *specificity* of the antibody was investigated by a crossed immunoelectrophoresis Only one pre ipitate can be observed (Fig 2)

The *precision* of the method was assessed by nterplate and intraplate variation The coefficient of variation for double estimations on different plates of the same samples (mean value = 167 mg/l S D = 9 5 mg/l and n = 37) was 5 8% and the coeffi cient of variation for double estimations on the same plate of one sample (*mean value* = *196 mg/l* S D = 5 0 mg/l and n = 15) was 2 7%



Fig 2 Crossed immunoelectrophoresis of 10 µl antigen standard diluted 1+1 In the first dimension electrophoresis (10 V/cm for 1 hour) the anode is to the right In the second dimension electrophoresis (? 5 V/cm for 20 hours) the anode is at the top SP$_1$ antibody concentration was 1% (v/v)

The *sensitivity* expressed as the smallest con centration which could be measured was about 8 mg/l (the sample diluted 1+3) Using 5 µl undiluted serum the sensitivity was about 2 mg/l

The *stability* of SP$_1$ was investigated on three samples from three pregnant women in the last trimester Sera were stored 8 days at −15 C 4 C and room temperature The results are given in Table II

Clinical results

The *reference interval* Since the number of SP$_1$ estimations during the course of pregnancy were rather small and since a Gaussian distribution of the estimations in the respective weeks could not be assumed 2 5 and 97 5 percentiles have been used

Table II *The stability of SP$_1$ in three samples stored 8 days at −15 C 4 C and room temperature*

Sample	−15 C (mg/l)	4 C (mg/l)	Room temp (mg/l)
1	156	156	156
2	244	252	264
3	104	104	104

Table III *The number of samples percentiles 2 5 50 and 97.5 in the different weeks of normal pregnancy*

Week of pregnancy	No of samples	Percentile 2 5 (mg/l)	50 (mg/l)	97 5 (mg/l)
8	19	3	5 5	8
10	20	3 5	6	14
12	12	14	16	20
14	17	18	20	33
16	14	21	28	36
18	15	20	28	51
20	17	25	34	47
22	17	28	32	52
24	15	37	46	59
26	18	44	60	87
28	15	47	72	96
30	20	64	76	125
32	20	79	116	152
34	20	76	142	191
36	20	80	183	293
38	20	100	199	292
40	20	92	138	225

(7) or rather a little bit higher and lower percentiles respectively A percentile is shifted upwards depending on n (the number of estimations) so that the probability is 0 025 that less than 2 5% of the ranked values in a given week of gestation are below the designated percentile *Similarly* a percentile is shifted downwards so that the probability is 0 025 that less than 2 5% of the ranked values are above the designated percentile (Table III) In Fig 3 the calculated percentiles are smoothed graphically SP_1 was detected as early as the eighth week The concentration increased moderately in ‑rst two trimesters but in the last trimester the was considerable A decrease was seen only in last week of the pregnancy In the last months of the pregnancy great differences between individuals was observed In the same figure serial SP_1 determinations on five pregnant women are shown It can be seen that the level of SP_1 for one pregnant woman taken up around the 24th–26th week relative to those of the four other pregnant women was maintained during the rest of the pregnancy The electroimmuno assay of serial samples from the pregnant woman with the highest levels of SP_1 is shown in Fig 4

Fig 5 shows the correlation between SP_1 and HCS on 82 samples evenly distributed from the 24th–40th weeks of pregnancy A positive correlation was found ($r = +0\ 64$)

The rate of *SP_1 disapperance from the ma‑* blood after the separation of the placenta at deli‑ ery was studied on two women (Fig 6) Samples were taken at the time of placental separation and at 12 hours intervals subsequently The curves are non linear and do not permit calculation of ha‑ time but the SP_1 concentration is decreased by about 45% 24 hours after separation of the placenta

Abruptio placentae For the two pregnant wo‑ men who developed abruptio placentae later in the pregnancy two SP_1 determinations were made i‑ the 36th–38th weeks The results were 80 mg/l a‑ 188 mg/l which were below and within the refer‑ ence interval At term caesarean section wa‑ performed on both women because of abnorm‑ fetal heart rates and vaginal hemorrhage The A‑ gar score after one minute was ten in both cases

Placenta previa Two SP_1 estimations were ma‑ on two samples from one pregnant woman in t‑ 37th and 38th weeks Both results were 138 mg‑ which was within the reference interval

Mild pre eclampsia SP_1 was estimated on samples from nine women with mild pre-ecl‑ There were no differences compared with norm‑ pregnancies in the 36th 38th and 40th wee‑ ($P>0\ 05$ by Mann Whitney s rank sum test) b‑ except in the case of one woman the results we‑ *below the 50th percentile An unchanged level w‑* observed in one woman from the 34th to the 3‑ weeks The placenta contained infarcts All the in‑ fants were liveborn with a birthweight of 2 500 g ‑ more and an Apgar score of 8–10 after one minu‑

Severe pre eclampsia 15 samples from th‑ women in the 33rd–40th weeks with severe p‑ eclampsia were studied The range was from 83‑

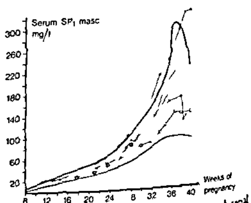
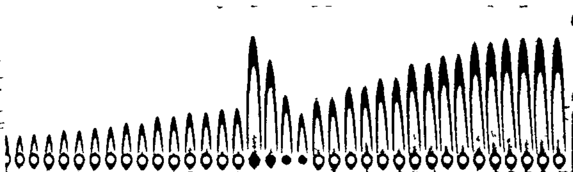


Fig 3 The reference interval for SP_1 and serial estimations from five pregnant women with a normal p‑ nancy



ig 4 Electroimmuno assay with serial samples from the regnant woman with highest level in Fig 2 ●=antigen andard dilutions (84 56 28 and 15 mg/l)

ng/l but apart from one estimation they were all ithin *the reference interval although below the* 0% percentile The birthweights were 2 200 g 500 g and 3 700 g respectively The Apgar scores fter one minute were 9–10

Chronic hypertensive disease Twelve serum amples from three pregnant women with hyperten ion were studied (Fig 7*a*) The range was from 23 o 100 mg/l No 2 in the figure showed a very small ise The delivery took place in the 28th week The nfant s weight was 1 010 g and the Apgar score after ne minute was six The next day the infant died of espiratory distress syndrome Nos 1 and 3 had early the same SP_1 concentration in the 35th–38th veeks and were in the lowest part of reference nterval The birthweights were 2 100 g and 3 150 g espectively The Apgar scores after one minute vere 9–10 HCS determinations on the same sam les are presented *in Fig 7b For no 2 an increas* ng concentration nearly up to the expected level in ormal pregnancy was seen

Neonatal asphyxia Analyses were carried out on 17 *samples from seven women who gave birth to* infants who showed symptoms of asphyxia after delivery (Fig 8*a*) Twelve results were scattered inside and five outside the reference interval In four of five cases where several samples were avail able from the same woman during the pregnancy a rise in the SP_1 concentration to the level expected in a normal pregnancy was observed The exception is no 4 but nos 3 and 7 whose infants had the lowest Apgar scores were below the reference in terval

Nearly all the corresponding HCS values (Fig 8*b*) fell in the reference interval including those for nos 3 and 7

Prematurity 36 samples from twelve women who delivered an infant weighing 2500 g or less were measured (Fig 9*a*) Information relating to the infant and the mother are presented in Table IV Congenital malformations were in three infants (mothers nos 2 7 and 11) In two of these cases the

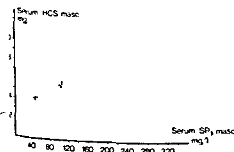


Fig 5 Correlation between SP and HCS concentration in 37 serum samples from pregnant women in the 24th–40th weeks ($y=0\ 043\ x+1\ 96$ $r=+0\ 64$ $P<0\ 001$)

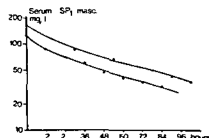


Fig 6 SP disappearance from maternal serum after the separation of the placenta Two cases are shown

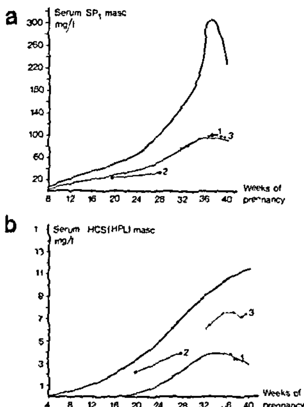


Fig 7 The serum concentration of SP_1 (*a*) and HCS (*b*) in three women with chronic hypertensive disease and the respective reference intervals

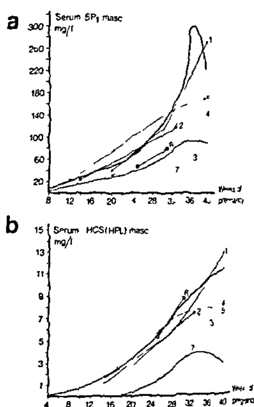


Fig 8 The serum concentration of SP_1 (*a*) and HCS (*b*) in seven pregnant women who gave birth to infants with neonatal asphyxia and the respective reference intervals

SP_1 level was above the reference interval (nos 2 and 11) In four women from whom samples were available after the 30th week and whose infants had birthweights of 2000 g or less and were without malformations the SP_1 results were below the reference interval (nos 4 5 6 and 10) Two women with considerable placental infarcts had a pronounced SP_1 fall at the end of the pregnancy (nos 8 and 12)

With regard to the corresponding HCS values

Table IV *Gestation age birthweight Apgar score and placental weight in women who delivered a premature infant*

Pregnant woman (no)	Week of pregnancy	Birth weight (g)	Apgar score 1 min after delivery	Placental weight (g)	Remarks
1	34–35	1 950	5	650	Danger of abortion in the 4th–5th months
2	28	1 475	3	570	Pulmonary tumor in the infant
3	40	2 300	7	–	
4	38–39	1 900	10	480	Infarcts and deg change in the placenta
5	36–37	1 700	9	400	
6	36–37	2 000	10	650	
7	35	1 600	6	–	Down s syndrome duodenal atresia
8	35	2 450	10	660	Large infarcts in the placenta
9	39	2 250	10	400	
10	32	1 510	–	–	
11	34	2 400	–	–	Congenital hydrocephalus
12	40	1 900	10	500	Infarcts in the placenta

able V *Fetal weight fetal changes placental weight and placental changes at fetal death*

regnant oman io)	Fetal weight (g)	Maceration	Placental weight (g)	Placental changes	Remarks
1	2 ?00	+	4?0	–	
,	274	+			
3	? 450	–	470	Deg changes	Low urine estrogens
4	950	+	4 0	Deg changes	
5	850	+	100	Necrosis	
6	850	+			An encirclage procedure was carried out in the 15th week
7					Spontaneous abortion
8	2 650	–	500	–	The mother had an impaired liver and renal function
9	3 500	–	560	–	
0	1 350	+	350	Deg changes	Low urine estrogens the umbilical cord twisted tightly round the neck
1					Spontaneous abortion in the 15th week

Fig 9*b*) the values for only one woman were elow the reference interval and showed a decreasing HCS concentration (no 5) A downward endency was also observed in three other cases nos 4 8 and 12)

Fetal death 26 SP_1 concentrations were measured in eleven women in whom pregnancy ended with the birth of a stillborn infant or in an abortion nformation relating to the fetus and the placenta are given in Table V and the SP_1 results are plotted n Fig 10*a* The SP_1 concentrations for several of the women were above the reference interval at irst but later on moved within the reference interval due to a small rise or fall of the SP_1 concentration (nos 1 2 and 4) A high SP_1 value was observed in one woman who six weeks later was admitted to hospital with hepatitis and who delivred while suffering from this disorder (no 8) For hree women the SP_1 values were below the reference range (nos 5 7 and 11) A rising SP_1 concentration as expected in a normal pregnancy occured in two cases (nos 3 and 10)

HCS determinations on the same samples (Fig 10*b*) showed a fall or lack of increase in concentration in three pregnant women (nos 1 4 and 5) whereas three women showed a rise nearly as great as expected in relation to the reference range (nos ? 3 and 10)

Hydatidiform mole SP determinations on five samples from three women with hydatidiform moles were carried out Only one SP value was within the reference interval while the others fell below this range Serial measurements of one woman showed decreasing concentrations Exactly the same relationship was seen in HCS estimations

Twin pregnancy SP_1 was measured on 26 samples from five women with twins Results for three women were outside the reference interval (nos 2

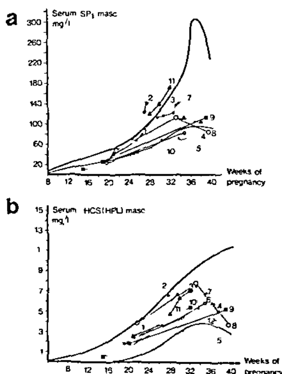


Fig 9 The serum concentration of SP (*a*) and HCS (*b*) in twelve pregnant women who delivered an infant weighing 2 500 g or less and the respective reference intervals

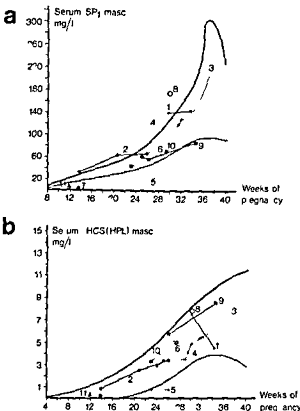


Fig 10 The serum concentration of SP_1 (*a*) and HCS (*b*) in eleven pregnant women in whom pregnancy terminated with a stillborn infant or an abortion and the respective reference intervals

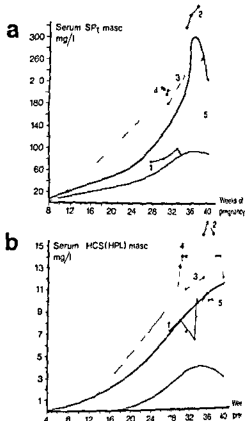


Fig 11 The serum concentration of SP (*a*) and HC in five pregnant women with twins and the resp reference intervals

3 and 4 in Fig 11*a*) In two cases the infant B died during and a short time after the delivery (nos 3 and 4) Two monochorionic pregnancies had the highest and the lowest SP_1 levels (nos 1 and 2) respective

It can be seen in Fig 11*b* that the HCS results ell above or in the upper part of the reference nterval

DISCUSSION

There are only a limited number of resports about the pregnancy specific β_1 glycoprotein (SP_1) (1–4 10 12–13) SP_1 is presumed to be secreted by the placenta and occurs only in connection with pregnancy

Storage experiments indicate SP_1 to be a thermostable protein which facilitates mailing of serum specimens and analyses in the laboratory

The turnover of SP_1 in maternal blood after delivery designated as the half life was determined by Bohn to be about 30–40 hours (3) and by Tatra et al to be about 34 hours (13) This estimate was confirmed by the current investigation where it was observed that the SP_1 concentration was n halved 24 hours after separation of the plac Therefore SP_1 is not suitable for detecting changes in placental function compared with whose half live is much shorter (about 15-20 Thus emergency testing for SP_1 is of no value

The rise of SP_1 in maternal serum during nancy is in agreement with Tatra et al (1?) the current investigation the SP_1 level was sl higher

To assess the clinical value of SP_1 estimati is logical to investigate the SP_1 serum levels in nancies terminating in fetal death In seven wo analysed with serial determinations two had a decrease three had a smaller increase than pected and two had an increase as expected compared to the reference interval An identic vestigation of HCS concentrations yielded re essentially the same as for SP_1 In the two c with normal SP_1 rise the 24 hours est oeen e tion was low In one case the cause was that umbilical cord was twisted tightly around the

one of three women in whom only one SP_1 estimation was performed the result was unexpectedly high Six weeks later she was admitted to hospital with hepatitis Laboratory tests showed that both liver and renal function were impaired Perhaps the explanation of the high SP_1 value is that the liver and/or kidneys influenced the SP_1 half life and the woman was subclinically affected at the moment of sampling In a group of pregnant women with fetal death Tatra et al found the serum SP_1 levels markedly reduced Most values lay below the mean −2 SD level and in addition showed a downward trend in two cases with several samples (12)

As for neonatal asphyxia the SP_1 values for two women whose infants had the lowest Apgar scores were below the reference interval The corresponding HCS values were in the lower part of the reference interval

For the women who delivered an infant of 2 000 g or less without congenital malformations the SP_1 results after the 30th week were below the reference interval The corresponding HCS results were within the reference interval except in the case of one woman Decreasing concentrations of both SP_1 and HCS were seen at the end of three pregnancies

For the five women who gave birth to twins the HCS results showed a tendency to be above or in the upper part of the reference interval than the SP_1 values

Of other discoveries in this study it should be stressed that the SP_1 values in pre eclampsia (except in the case of one woman) and in chronic hypertensive disease were in the lowest part of the reference interval This is in accordance with Tatra et al (12) They found the maternal SP_1 values in pregnant women with pre-eclampsia without essential fetal or placental impairment fell within the normal range but below the mean value of normal pregnancies It is obvious that these pregnancies belong to the group of high risk pregnancies resulting from reduced placental function

Generally information about changes in the placental function in a pregnant woman could be obtained by serial determinations and by observing percentile deviation later on in the pregnancy

In conclusion SP_1 may possibly be a valuable parameter for monitoring and discovering pathological pregnancies Larger investigations must be performed to decide whether SP_1 determinations will provide earlier and more extensive information than currently used hormone analyses

ACKNOWLEDGEMENTS

The present work is an extract from an entry for a prize paper set by the University of Copenhagen Denmark and which was awarded the Gold Medal of the University

The antiserum was kindly supplied by Behringwerke

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Submitted for publication Aug 11 1976

S Sørensen
Bavnestedet 85
DK 3500 Værløse
Denmark

Acta Obstet Gynecol Scand 57 203–209 1978

EXTREMELY LOW PLACENTAL LACTOGEN HORMONE (hPL) VALUES IN AN OTHERWISE UNEVENTFUL PREGNANCY PRECEDING DELIVERY OF A NORMAL BABY

Preben Gaede Dyre Trolle and Henning Pedersen

om the Departments of Obstetrics YA and G and the Department of Clinical Chemistry ML (Hormone Laboratories) University of Hospital of Copenhagen Rigshospitalet and Herlev Hospital Copenhagen Denmark

stract A case of a normal pregnancy and delivery with tremely low placental lactogen hormone (hPL) values in aternal blood is presented The low hPL-values were e to the fact that the placenta only produced about 1/25 the normal estimated output calculated on the basis of hPL-concentration in the invervillous spaces The ncentrations of progesterone the placenta specific glycoprotein (SP_1) and total estriol in serum were nor al while prolactin and chorionic gonadotropin (hCG) re considerably elevated Glucose levels were normal the ultrastructural level the actual placenta under study d not differ from a normal term placenta In spite of the ry low concentrations of hPL there was a good milk cretion and the mother was still breast feeding her baby months after the delivery Basal level of prolactin was this time normal

uring the past five years the hormone human pla ntal lactogen (hPL) has routinely been de rmined in the serum of 20 000 pregnant women

hPL is a specific placental hormone developed in e syncytiotrophoblast in increasing quantities as egnancy proceeds The hormone is to be found in e blood but not in the urine probably due to the t that it is degraded in the maternal kidneys (2)

Values *above* the reference interval are observed cases of large placenta e g large fetus multiple egnancy diabetes mellitus and Rhesus immuni ation Furthermore high values are found in omen with renal failure due to insufficient degra tion (4)

Values *below* the reference interval are found in sociation with low values of urine and serum triol in cases of placental insufficiency in auterine fetal death or miscalculated length of egnancy Low values of hPL combined with nor al values of estriol are seen in an early stage of acental insufficiency (4)

During the five year period in which we have plied the hPL analysis routinely we have only ice found extremely low hPL values in an oth erwise completely uneventful pregnancy The case is hereby reported

CASE REPORT

The patient was a 27 year-old primigravida whose last menstrual period was 14 2 1975 and who first felt fetal movements on 10 7 1975 Her expected date of delivery was 21 11 1975 Her pregnancy proceeded entirely un eventful apart from the reported hormonal values The extremely low hPL values are shown in Fig 1

Due to an estimated fetal weight of 3 800 g and to the fact that the patient was at term medical induction of labour was performed on 21 11 and that same day a normal boy was delivered weighing 3 740 g length 54 cm Apgar scores were 10 after one and five minutes The boy did not show any sign of abnormality He was breast fed and mother and child were discharged from the hospital on the sixth day The boy thrived and his weight at the time of discharge was 3 760 g The placenta weighing 6?0 g was macroscopically and microscopically normal Further more the placenta was examined by electron micro-scopy which will be referred to at a later stage

The boy was examined at the age of 11 months and he was physically and mentally normal He weighed 10 8 kg and measured 76 5 cm in length He was still being breast fed and the mother stated that she produced ample amounts of milk in spite of the fact that she had started employment outside her home At this examination she reported having menstruated (irregularly) on three occa sions since the delivery

MATERIALS AND METHODS

Maternal blood samples were drawn from an antecubital vein between 8 and 10 a m and analysed for hPL the same day Afterwards the serum samples were stored at −20°C for subsequent analyses for estriol progesterone pro-lactin hCG and a placenta specific β glycoprotein (SP_1) (1)

Blood samples from aa and v umbilicales and the in tervillous cavities were drawn by a special technique Immediately after the delivery a piece of the umbilical cord about 15– 0 cm was isolated with altogether four clamps (see Fig 2) It is essential that this process is carried out as soon as possible in view of the fact that the aa umbilicales are emptied very quickly after delivery By cutting the umbilical cord between the two sets of clamps (Fig 2 (*a*) and (*b*) the filled section of the umbilical cord

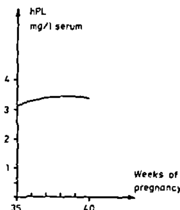


Fig 1 The extremely low hPL-values in the last part of pregnancy The solid line is the lower limit of the 90% reference interval

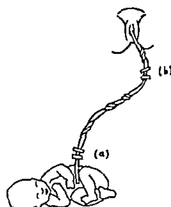


Fig 2 The special technique used for collecting bl from the aa and v umbilicales separately The umb cord is cut between the clamps at (a) and (b)

was isolated It was carefully dried with a piece of gauze (moistened with physiological saline) before collection of the blood samples A hypodermic needle mounted on a syringe was then introduced into the v umbilicalis which was first emptied and subsequently into the two arteries which were now very distinct and readily emptied

At the delivery of the placenta the membranes were carefully gathered round the placenta which was then placed in a large glass funnel A few minutes later blood had collected between the cotyledons and a blood sample could readily be withdrawn with a syringe This blood must be supposed to originate from the intervillous spaces of the placenta and is referred to as such in the following

SP_1 and hPL in serum were determined by immunoelectrophoretic methods described in general by Nørgaard Pedersen & Gaede (3)

Serum prolactin hCG and estriol were all measured by specific radioimmunoassays Progesterone was measured by a competitive protein binding method

Preparation for electron microscopy

Immediately after delivery of the placenta small tissue samples from different locations throughout the thickness of the chorionic plate were fixed in collidine buffered glutaraldehyde for two hours and after a short buffer r postfixed in collidine buffered osmiumtetroxide for other hour After dehydration in graded concentra of ethanol and propyleneoxide the tissue was embedd Epon 812 Thin sections were stained with uranyl acet and lead citrate and examined in a Philips 301 elec microscope

RESULTS

Fig 1 shows hPL in serum during the last th weeks of pregnancy the inserted line indicating lower limit of the 90% reference interval for hPL normal pregnancies (2)

Table I shows the concentrations of hCG p gesterone SP_1 prolactin glucose and total estr in serum samples from the 38th 39th and 40th w of pregnancy

Table II shows the concentrations of serum h in the aa and v umbilicales and the interv spaces the respective reference intervals bein

Table I *The hormone concentrations in maternal serum during the last three weeks of pregnancy*
While the hPL values are extremely low both hCG and prolactin show greatly elevated concentrations Progeste SP_1 and total estriol are all within the normal range for this stage of pregnancy

	hPL (mg/l)	hCG (i u /l)	Pro-gesterone (nmol/l)	SP_1 (mg/l)	Total estriol (μmol/l)	Prolactin (μg/l)	Gluco (mmol
38th week	0 4	119 700	530		0 65		4 6
39th week	0 7	103 000	760	160	0 69	ca 2 700	
40th week	0 6	109 500	810	195	0 80	ca 2 700	
11 months p p						65	

Normal range for *hCG* 4 000–32 000 i u /l (38th–40th week)
Normal range for *prolactin* 50–600 μg/l (38th–40th week) 80–150 μg/l (lactation period)

ble II *Serum concentrations in aa and v mbilicales of hPL showing together with the concentration in the intervillous spaces an extremely production of hPL in the actual placenta*

	Serum hPL-concentration (mg/l)
iternal	0 7 (see Fig 1)
and v umbilicales	<0 001 (0 01–0 03)
ervillous spaces	0 9 (25–37)

e concentration range shown in the brackets were culated on the results of serum samples from five de nes with normal hPL-concentrations in ma ernal um

ated on the basis of serum samples from five liveries with normal maternal serum hPL ncentrations

ctron microscopy

general ultrastructure of the term human enta has been described in several reports with niques of preservation changing through the s Due to very elaborate ultrastructure of the hoblast particularly the syncytiotrophoblast to the fact that the substructural details are high ependent on the preservation technique normal n placentae were examined for comparison and be referred to as the normal controls

yncytiotrophoblast In the placenta with ex nely low production special attention was given the endoplasmic reticulum of this cell Both ooth and rough endoplasmic reticulum appeared pproximately equal proportions when the actual centa was compared to the normal ones Usually re was a layer of smooth endoplasmic reticulum eath the maternal surface of the cell (Fig 3) and the interior of the cell areas appeared with itly packed rough endoplasmic reticulum (Figs 3 1 4) The superficial smooth endoplasmic re ulum was of the flattened reticular type and only ess well preserved cells did it show up as vesicu elements Both types of the endoplasmic re ulum had a fine granular content In the control centae the smooth superficial endoplasmic re ulum occasionally appeared as fenestrated lamel (Fig 9) sometimes with a peculiar organization g 8) which has also been observed in human pora lutea Such structures were not observed in actual placenta associated with low hPL duction

In the actual placenta the mitochondria under investigation were found in the interior of the cell often in close relation to the rough endoplasmic reticulum (Figs 3 and 4) In number location and substructure the mitochondria of the normal con trols did not appear to differ significantly

In both the normal controls and the actual syncytiotrophoblast cells the cytoplasm contained microfilaments vesicular elements of different appearance lipid droplets (Fig 5) and superficially coated vesicles and rounded membrane bound bodies with a dense homogeneous content (Figs 3 7 8 and 9) Centrioles were seen (Fig 3 inset) and often desmosomes were recognized within the cytoplasm apparently without any connection with the plasma membrane (Fig 7)

Golgi complexes were encountered throughout the cytoplasm but preferentially in the superficial cytoplasm and occasionally with dense material between its cisternae (Fig 7) The maternal surface of the cell was characterized by the presence of numerous microvilli

The nuclei had an irregular outline with pe ripheral clusters of heterochromatin in which light areas corresponded to the position of the nuclear pores (Fig 5)

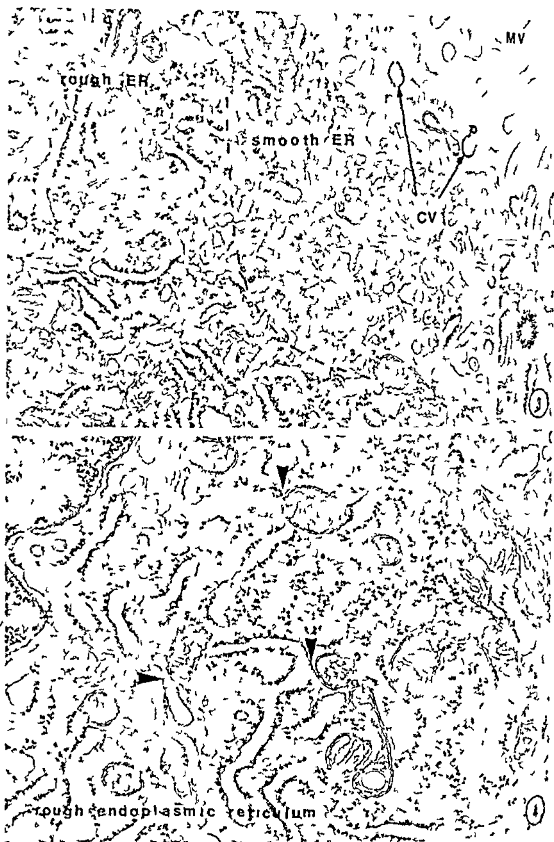
Cytotrophoblasts These cells were easily rec ognizable by their light cytoplasm with large mitochondria scattered rough endoplasmic reticulum

Fig 3 From the actual placenta with extremely low hPL production Beneath the maternal surface of the syn cytiotrophoblast characterized by the microvilli (*MV*) and coated vesicles (*CV*) there is a layer of smooth endoplasmic reticulum Deeper in the cell rough endoplasmic reticulum predominates Inset centriole

Fig 4 The mitochondria of such a cell (see Fig 3) are closely related to the elements of the rough endoplasmic reticulum (arrow heads)

Fig 5 In the cell type similar to the one shown in Fig 4 the perinuclear cytoplasm is poorly provided with endoplasmic reticulum but dominated by bundles of microfilaments (*MF*) and smaller vesicular and membraneous elements Dispersed throughout the cell lipid droplets (*LD*) can be recognized There is a normal distribution of heterochromatin in which light areas correspond to the nuclear pores (arrow-heads)

Fig 6 The cytotrophoblast from the placenta with ex tremely low hPL concentration also has a normal substructure The mitochondria are also in this cell type closely related to the profiles of rough endoplasmic reticulum (arrow heads) The cytoplasm is light with much fewer organelles than seen in syncytiotrophoblast cells Microfilaments and microtubules are seen evenly dispersed in the cytoplasm (*MF* and *MT*)


MV
rough ER
smooth ER
CV
3
rough endoplasmic reticulum
4

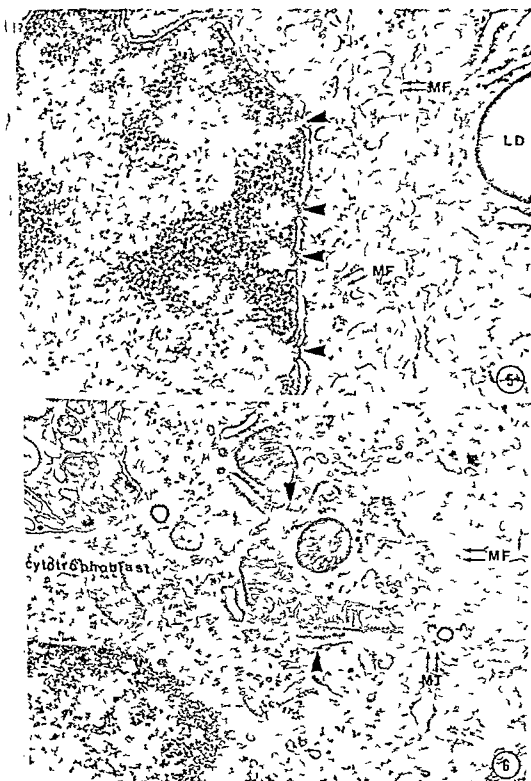

MF
LD
MF
5
MF
cytotrophoblast
MT
6





Fig 7 In normal placentae as well as in the actual one Golgi complexes were found mostly in the maternally oriented part of the cell and sometimes a dense material was interposed between the lamellae of this complex (arrows) Intracellular loose desmosomes were often observed (encircled)

Fig 8 In normal syncytiotrophoblast the [illegible] reticulum was seen to be arranged in a peculiar [illegible] structure (between arrow heads) a feature which [illegible] observed in the actual placenta under investigation [illegible]
Fig 9 Another structure that was only seen in [illegible] placentae was fenestrated lamellae

icrotubules microfilaments and glycogen (Fig 6) sually the rough endoplasmic reticulum was osely related to the mitochondria In outline and ibstructure of the nuclei the normal controls did ot seem to differ from the actual cells Also in this ll type there seemed to be no significant difference between the normal placentae and the actual ie

DISCUSSION

ormal pregnancy and delivery with extremely low PL-values during the last part of pregnancy have our knowledge not previously been reported As will appear from Table II the low maternal hPL alues were due to the fact that the placenta only roduced about 1/25 its normal output estimated n the basis of the hPL concentration in the in rvillous spaces

Of the other hormone concentrations in the maternal blood SP_1 estriol and progesterone were ormal while prolactin and also hCG were greatly icreased Also glucose levels were normal A lood sample drawn from the mother 11 months fter the delivery and while she was still breast eding showed a normal basal level of prolactin t this time there had been three (irregular) menrual like periods It should be emphasized that iroughout the period after delivery milk secretion has been adequate

At the ultrastructural level the actual placenta id not differ from normal term placenta The mount of cytoplasmic and nuclear elements their itracellular location their individual interrelationship and their substructure seemed to be ormal In the normal placentae however festrated lamellae and a whirled arrangement of smooth endoplasmic reticulum were recognized casionally features which were not observed in actual placenta The functional significance of ch modifications of the endoplasmic reticulum is present unknown but it seems unlikely that their casional presence should be of any significance ch respect to the production of the large amounts hPL in normal pregnancies Thus from a orphological point of view this functional defect in actual placenta viz the almost complete lack of hPL production is not associated with significant cytological changes at least with the present quality of cell preservation

Perhaps one might not expect that a deficient production of a single protein hormone even as pronounced as in this case should be reflected in morphological changes in cells with such a multitude of functions as the trophoblast cells

CONCLUSION

The purpose of the present study was to show that it was possible to carry through a normal pregnancy and delivery in spite of an extremely low hPL production in the placenta The newborn child in question was entirely normal and showed no signs of physical or mental abnormalities at the age of 11 months The mother had excellent milk secretion and was still breast feeding her baby 11 months after the delivery The explanation might be found in the concentration of prolactin which was considerably increased before the delivery but normal 11 months later at the post examination

ACKNOWLEDGMENTS

We are grateful to Dr Claus Hagen and Dr Peter Schultz Larsen for the prolactin and SP analyses respectively The investigation was supported by the Danish Medical Research Council (Grant no 512 2747)

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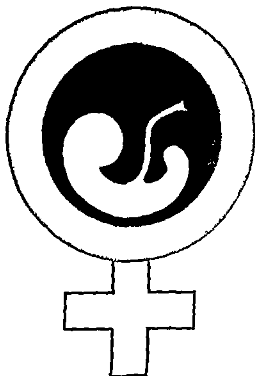
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Preben Gaede
Dept of Clinical Chemistry ML
University Hospital of Copenhagen
Rigshospitalet
Copenhagen
Denmark

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Acta Obstet Gynecol Scand 57 211–215 1978

THE VALUE OF SERUM CYSTINE AMINOPEPTIDASE (CAP) HUMAN CHORIONIC SOMATO MAMMOTROPHIN (HCS) AND URINARY OESTROGEN ASSAYS FOR DETECTING INTRAUTERINE GROWTH RETARDATION

Gunnar Ryden

From the Department of Obstetrics and Gynecology University Hospital Linkoping Sweden

bstract The aim of the present study was to compare the sefulness of cystine aminopeptidase (CAP) and human horionic somato-mammotrophin (HCS) estimations in naternal serum and maternal urinary oestrogen excretion n predicting intra uterine growth retardation The mate ial consists of 43 patients who subsequently gave birth to nfants with a birth weight less than 2 S D from the mean ccording to the gestational age The patients were conrolled with simultaneous analyses of CAP HCS and urinary oestrogen assays every week from the 36th week f pregnancy The patients have been compared with nother group in which infants with normal birth weight nd without signs of fetal distress were delivered Intrauterine growth retardation (IGR) was predicted by low estrogen levels in 58% low HCS levels in 42% and low AP levels in 35% The difference between the biochemi al tests was not statistically significant IGR infants who eveloped fetal distress were predicted by oestrogen as ays in 77% by HCS assays in 62% and by CAP assays in 8% If urinary oestrogen assays were combined with ICS assays this combination predicted IGR significantly etter than oestrogen assays alone The combination ICS–CAP was as informative in this respect as urinary estrogen assays alone The results indicate that all iethods tested are rather insensitive in predicting the otal number of IGR infants The capacity for predicting GR infants with fetal distress is however rather high or this purpose a combination of tests is preferable as no est fulfils the qualifications of being superior to the other The combination oestrogens–HCS seems to be most uitable in this respect

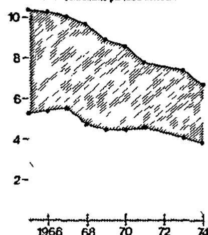
review of mortality data from Sweden demon trates a decreasing perinatal mortality during the ast decade down to 1 3–1 4% (Fig 1) The number f deaths during delivery and the neonatal period in cent years are mostly due to immaturity and nalformations Among the stillborn infants which re responsible for about 50% of the mortality here is an excess of small for-date babies About 0% of these infants weigh less than one S D from he mean according to the gestational age (5) A further decrease in perinatal mortality might there fore be possible if better supervision of the preg nant women could be arranged during the last trimester in order to detect intrauterine growth re tardation Many different methods for evaluating the feto-placental unit during the last trimester have been published which indicate that no single test is perfect Among the chemical methods in use measurements of urinary oestriol or total oes trogen excretion estimation of human chori onic somato mammotrophin (HCS) and cystine aminopeptidase (CAP) in maternal plasma seem to be the most widely used methods

The aim of the present study is to compare the usefulness of all three chemical methods in predict ing intrauterine growth retardation

MATERIAL

The material has been selected from about 800 "at risk" pregnancies which were monitored by simultaneous analyses of CAP HCS and urinary oestrogens usually with weekly intervals from the 36 week of pregnancy The series consists of 43 patients who subsequently gave birth to infant with a birth weight less than 2 S D from the mean according to the gestational age The patients were collected during the period 1 Jan 1973 to 31 Dec 1975 During that time the total number of deliveries was 6785 with a perinatal mortality of 1 15% The small-for-date series has been divided into one group (A) including 22 patients without complications during delivery and another group (B) including 21 patients where fetal distress was observed at delivery (Apgar score less than 7 one minute after delivery or where the indication for operative delivery was fetal distress) Among the 43 pa tients studied in this way there was no perinatal death

The small for-date" group has been compared with a series of 540 "at risk pregnancies collected during the period 1 Jan 1973–31 Dec 1974 when the pregnancies were monitored in the same manner These patients sub-



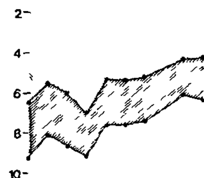


Fig 1 Perinatal mortality in Sweden 1965–1974 No figures are available for 1972 owing to change in account from the hospitals to the Medical Board The bright area indicates infants with birth weight <2 500 g and the dark area birth weight ≥2 500 g

sequently gave birth to single infants with normal birth eights and without signs of fetal distress during delivery Patients who delivered infants with an Apgar score of less than 7 or where operative delivery was required for fetal distress (a total of 81 patients) have been excluded from the control group

METHODS

The daily urinary output of total oestrogens was measured according to Hainsworth & Hall (7) The determinations were performed with a Technicon autoanalyzer Cystine aminopeptidase (CAP) in serum was measured at 37°C with the method described by Peeters (9) using 1 cystine bis para nitroanilide as substrate Human chorionic somato-mammotrophin (HCS) was measured according to Letchworth et al (8) whereby the Phadebas HCS Kit from Pharmacia Diagnostics was used

Low biochemical parameters have been defined as follows

HCS <4 mg/l serum from the 36 week of pregnancy
CAP <80 nkat/l (4 8 U/l) serum from the 36 week of pregnancy

Urinary oestriol excretion
<70 μmol (20 mg)/24 hours during pregnancy week 36–37
<84 μmol (24 mg)/24 hours from 38 week of pregnancy

The statistical analyses performed were based on Fisher's exact test for two×two tables (See Brownlee 1965)

RESULTS

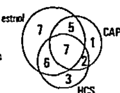
The incidence of low biochemical parameters among *women who delivered normal* infants and small for date infants are presented in Table I

As demonstrated oestrogen assays seem to be somewhat superior to CAP or HCS assays in predicting growth retarded infants In 58% of the women who delivered growth retarded infants low oestrogen values were found in comparison to 42 and 35% for HCS and CAP respectively The figures obtained are rather low and indicate that the biochemical methods are rather insensitive in predicting intrauterine growth retardation

However a comparison between small-for-date infants with uncomplicated deliveries and fetal distress clearly shows that the chemical assays and

Table I *The incidence of low biochemical values in women who delivered growth retarded infants and normal infants respectively*

	Normal infants		Intrauterine growth retardation					
			Totally A+B		Uncomplicated delivery (A)		Fetal distress (B)	
	n	%	*n*	%	*n*	%	*n*	%
Number of patients	540		43		22		21	48
Low CAP	29	5 4	15	35	5	23	10	6.
Low HCS	30	5 6	18	42	5	23	13	7'
Low oestrogens	47	8 7	25	58	10	46	15	



ig 2 The number of low biochemical tests with different combinations of tests in 43 mothers who delivered small or-date infants

specially oestrogen assays to a large extent pre ict the complicated cases

A statistical analysis was performed in order to ompare the usefulness of the methods in predicting ntrauterine growth retardation No significant dif rence was found in the total series (A+B) between he biochemical tests studied Concerning the sub- roups of uncomplicated delivery (A) and small or-date infants with fetal distress (B) the numbers re too small to allow a statistical analysis

In order to study if a combination of tests give ore information than only one test the incidence f low biochemical parameters have been calcu ated for the different combinations used The umber of low values when using different combi ations of the biochemical tests are presented in ig 2 and Table II A statistical analysis on the otal series (A+B) was performed to evaluate whether oestriol combined with HCS or CAP is ore informative than oestrogen assays alone estrogen–HCS was significantly better than estrogen alone ($P=0\ 003$) whereas when estrogen–CAP was compared with oestrogens lone no such difference was found ($P=0\ 07$)

The results obtained with different combinations f tests are rather equal The combination HCS–CAP seemed to be less informative than the other combinations A comparison between the combination oestrogen–HCS and HCS–CAP could however not demonstrate a significant difference in favour of oestrogen–HCS ($P=0\ 49$)

DISCUSSION AND CONCLUSION

Intrauterine fetal growth retardation secondary to placental insufficiency is responsible for a significant proportion of perinatal deaths in modern obstetrics (5) In order to detect placental insufficiency at an earlier stage of gestation different hormonal and enzyme assays have been suggested In a recently published review Biggs (1) pointed out that opinions vary about the clinical significance of different assay procedures and oestrogen assays seem to be the yardstick against which many other tests are measured In the present study urinary oestrogen assays were found to be the most useful for the prenatal diagnosis of growth retarded infants whereas HCS and CAP estimations were of similar value in this respect The differences between the three methods were rather small and not statistically significant Urinary oestrogen assays have however some limitations the need for a 24-hour urinary sampling and the large day to-day variation HCS and CAP assays are easier to perform the day to-day variation is less and they are therefore more suitable for routine use The recent introduction of quick radio-immunoassay procedures for free or total oestriol in serum and/or urine might however change the picture in this respect Compared with radio-immunoassay procedures however the spectrophotometric method for CAP assays is considerably less expensive If HCS and CAP were used together they predicted intrauterine growth retardation as effectively as urinary

able II *The incidence of low biochemical values with different combination of tests*

	Normal infants		Intrauterine growth retardation: Totally A+B		Intrauterine growth retardation: Uncomplicated delivery (A)		Intrauterine growth retardation: Fetal distress (B)	
	n	%	*n*	%	*n*	%	*n*	%
umber of patients	540	43	22	21				
ow CAP or oestrogens	73	14	28	63	11	50	17	81
ow HCS or oestrogens	73	14	29	70	12	55	18	86
ow HCS or CAP	52	9 6	24	56	9	41	15	71
ow HCS CAP or oestrogens	93	17	31	72	12	55	19	91

oestrogen assays In the present study only patients examined from the 36th week of pregnancy were included in the study It has been shown by Ryden (12) that CAP values generally decrease before oestrogen values in placental insufficiency and the same might be valid also for HCS Studies performed earlier in gestation might therefore show some advantage for HCS and CAP assays in comparison with oestrogen assays for the early diagnosis of intrauterine growth retardation Petrucco et al (10) who compared oestriol and CAP assays in predicting intrauterine growth retardation found CAP to be superior to urinary oestriol assays in this respect The difference was only obvious between 28–35 weeks of gestation CAP and HCS however only reflect the condition of the placenta This implies that these methods cannot be a substitute for oestriol assays in monitoring at risk pregnancies but can be used as valuable tests for detecting growth retarded infants with an increased risk of fetal distress No statistically significant difference was found between CAP and HCS assays in this respect The at risk pregnancies detected in this way should be studied further with more sensitive indicators of fetal well being i e oestriol assays CTG curves oxytocin challenge tests

It is possible that more information can be gained by serial assays of CAP in order to construct a curve and calculate the minimum and maximum allowable gradients for the change in enzyme activity In that way Chapman et al (3) were able to predict small for date babies (less than the tenth for gestational age) in 78% They concluded that the gradient of CAP readings are more important than the actual enzyme levels From the clinical point of view a calculation of CAP gradients should increase the number of normal infants who where predicted as small for dates and it is therefore questionable if such calculations should offer any advantages It should however be emphasized that rapidly increasing or decreasing levels of CAP might indicate an imminent intrauterine death of the fetus (11)

The incidence of low oestrogen values among small for date pregnancies in the present study (58%) is somewhat less than 72% obtained by Curzen & Varma (4) This is partly due to different criteria for low oestrogen excretion and partly to the definition of growth retardation Thus Curzen & Varma found 21% low oestriol assays in normal birth weight infants compared to 9% in the present study They defined intrauterine growth retard[illegible] as a birth weight below the tenth percentile as compared with less than 2 S D from the mean in the present study This latter fact also explains why Edwards et al (6) obtained low HCS levels in [illegible] of the growth retarded infants compared to [illegible] in the present study

The high incidence (45%) of normal biochemical values in the group of growth retarded infants without fetal distress might indicate at least two different groups of growth retarded infants one group possibly genetic with normal placental function normal biochemical tests and a low risk of complication during delivery and another group with placental insufficiency low biochemical levels and a high risk of complications during delivery and the neonatal period It can be emphasized that [illegible] the biochemical tests are unreliable in de[illegible] total number of growth retarded infants all [illegible] methods are valuable in detecting those where fetal distress can be expected

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Submitted for publication Nov 4 1976

Gunnar Ryden
Department of Obstetrics and Gynecology
University Hospital
581 85 Linkoping
Sweden

Acta Obstet Gynecol Scand 57 217–221 1978

ANTEPARTUM ADMINISTRATION OF TERBUTALINE AND THE INCIDENCE OF HYALINE MEMBRANE DISEASE IN PRETERM INFANTS

B Bergman and T Hedner

From the Department of Obstetrics and Gynaecology Centrallasarettet Molndal Sweden

bstract The incidence of hyaline membrane disease in preterm infants born between January 1975 and nuary 1976 was investigated in a retrospective study rbutaline a beta$_2$-receptor stimulating drug had been ministered to the women in order to arrest premature bour In spite of the treatment 24 preterm infants were livered The incidence of HMD in this group was 1/24 a group of 17 neonates whose mothers had received no h treatment the incidence of HMD was 5/17 Comparison between the two groups revealed a significantly lower idence of HMD in the terbutaline treated group than in controls ($p<0.05$) There were no significant differ es in maternal age gestational age birth weight or gar score between the two groups The lower incidence HMD in the terbutaline treated group is suggested to lect a rapidly induced release of pulmonary surfactants the preterm infants Evidence for a similar sequence of nts has earlier been shown to occur in animals under ndardized experimental conditions

e of the major hazards of preterm infants is the velopment of idiopathic respiratory distress drome (IRDS) or hyaline membrane disease MD) A growing number of reports have been blished concerning the prediction and prevention HMD In a controlled trial Liggins & Howie (10) wed that antepartum administration of glucocor steroids to the mothers lowered the incidence of piratory distress syndrome of premature neon s This observation was confirmed in an expand study (6) and subsequently also by other investi ors It should however be noticed that Liggins Howie in their trial actually used a combination corticosteroids and drugs known to induce re ation of the uterus either sympathicomimetics ethanol Other drugs as thyroxine and heroine e also been reported to lower the incidence of piratory distress syndrome (5 15) Kero et al (7) l not observe any case of respiratory distress drome in 38 premature children whose mothers have been treated with isoxsuprine during labour A new category of drugs with selective beta$_2$-receptor stimulating effects as ritodrine salbutamol and terbutaline has become available during recent years for suppression of uterine contractility (1 8 11) These drugs are extensively used in cases of threatened abortion threatened premature labour and uterine hypercontractility during term labour In a retrospective study Boog et al (3) found a reduced incidence of respiratory distress syndrome in premature infants following ritodrine administration to the mothers The difference was only significant in infants weighing less than 2300 g compared with controls of equivalent weight In this study we have investigated the effect of a beta$_2$-receptor stimulating drug terbutaline on the incidence of HMD in preterm infants

PATIENT MATERIAL AND METHODS

Fourty-one live born preterm infants delivered in the department between January 1975 and January 1976 were included in this study The routine of the department in the management of preterm labour is administration of terbutaline orally or intravenously Twenty four infants were born before 36 completed weeks of gestation although the mothers had received terbutaline Doses and administration routes appear in Table IV

In some instances of preterm labour the mothers were not treated with terbutaline or any other beta receptor stimulating drugs because of advanced labour at admittance to the hospital (7 infants) rupture of membranes at admittance to the hospital and delivery within 1 hours (6 infants) placenta praevia with hemorrhage (2 infants) signs of placental insufficiency (1 infant) and miscalculation of gestational age (1 infant) These 17 infants delivered by 15 mothers served as controls

None of the mothers had received corticosteroids isoxsuprine thyroxine heroine or any other drugs earlier reported to stimulate fetal lung maturation premature rupture of membranes more

Table I *Details of the terbutaline treated group*
VD=Vaginal delivery CS=Caesarian section

Gestational age (weeks)	Maternal age (years)	Birth weight (g)	Terbutaline adm route	Apgar score	Sex	Delivery	HMD	Obstet comments	Pediatr comments
30	23	1 500	i v +o	9	M	VD	–	Cerclage	
30	27	1 650	i v	7	M	VD	–	Indomethacin 300 mg	
31	28	1 750	i v	7	M	VD	–	Indomethacin 100 mg	
31	19	1 910	i v +o	6	F	VD	–		
31	29	2 210	i v +o	8	M	VD	–	Vacum extr	Immin asphyx
32	29	1 890	i v	3	M	VD	–	Indomethacin 300 mg	
33	27	1 590	o	10	F	VD	–	Multiple pregnancy	2 nd twin dead antepartum
33	19	1 940	i v +o	8	M	CS	–	Multiple pregnancy diabetes	
33	19	2 410	i v +o	7	M	CS	–	Multiple pregnancy Diabetes	
33	18	1 680	i v +o	7	M	VD	–		
33	19	1 650	i v +o	7	M	VD	–	Cerclage	
33	32	1 850	i v	7	M	CS	–	Ablatio plac	
33	34	2 260	i v	9	F	CS	HMD	Acute periapp	
34	29	2 070	i v +o	8	F	VD	–	Vac extr Cerclage	Immin asphyx
34	28	2 200	i v +o	8	M	VD	–	Cerclage	
35	26	2 420	i v	7	M	VD	–		
35	36	2 410	i v	4	M	VD	–		Listenosis, dead after 3 days
36	23	2 435	i v +o	10	F	VD	–	Cerclage	
36	26	2 300	o	9	F	VD	–	Cerclage	Heart malformation
36	27	2 210	i v +o	10	F	CS	–	Multiple pregnancy Cerclage	Breech
36	27	1 820	i v +o	8	F	CS	–	Multiple pregnancy Cerclage	
36	23	1 850	i v +o	10	M	VD	–	Cerclage	
36	29	2 250	i v	10	M	VD	–	Toxemia	
36	26	2 440	i v +o	10	M	CS	–	Earlier hysterotomy	

fore delivery were excluded Also excluded was one neonate in the terbutaline treated group who died within 2 hours post partum weighing 920 g and with a gestational age of 26 weeks Unfortunately autopsy was not performed but no clinical signs of HMD were reported in this case The preterm infants included in this study had a weight of 2 500 g or less

All children were immediately taken to the neonatal intensive care unit observed given identical care and treated if complications developed The diagnosis of HMD was based on the respiratory rate grunting chest retraction increasing demand for oxygen on radiological signs and on autopsy findings The gestational age was based on menstrual history uterine size ultrasound scans radiological examinations during pregnancy birth weight general appearance body dimensions and neurological development at medical examination carried out immediately after birth (14) The Apgar score was recorded one minute after delivery and the weight of the infants were measured before or shortly after the transport to the neonatal intensive care unit

Statistical analysis of the data included the χ^2 test and Student s *t* test

RESULTS

Details and clinical data of the terbutaline tre[illegible] group and the control group appear in Tables I [illegible] II In the terbutaline group 24 infants were de[illegible] livered by 22 mothers One infant in this [illegible] showed typical signs of *HMD* *Of the 17 in*[illegible] delivered by 15 mothers in the control group [illegible] was noted in 5 neonates Comparison between the two groups revealed a significantly lower [illegible] of HMD (p<0 05) in the terbutaline group Th[illegible] mean gestational age in the *terbutaline group* [illegible] 33 6±0 5 weeks (mean±S E M) ranging [illegible] 30 and 36 weeks The neonates of the control [illegible] had a gestational age between *31 and* [illegible] mean 34 7±0 4 weeks The difference between [illegible] two groups was not significant Compared with [illegible] control group a greater proportion of the infa[illegible] the terbutaline group had a gestational age of [illegible] weeks or less In this subgroup one of 13 infants

Table II *Details of the control group*
VD=vaginal delivery CS=Caesarian section

Gestational (weeks)	Maternal age (years)	Birth weight (g)	Apgar score	Sex	Delivery	HMD	Obstet comments	Pediatr comments
	19	1 470	3	M	VD	–		
	?4	1 570	7	M	VD	HMD	Multiple pregnancy	Dead after 27 hours
	24	1 400	3	M	VD	HMD	Multiple pregnancy	Dead after 16 hours*
	35	1 960	9	M	CS	HMD	Plac praevia	
	?6	1 890	9	M	VD	–		
	?0	2 180	10	F	VD	–		
	25	2 040	8	F	CS	–	Plac praevia	
	23	2 170	10	M	VD	HMD		
	24	2 480	10	F	VD	–		
	34	2 230	8	M	CS	HMD	Narrow pelvis	
	?7	2 290	10	F	VD	–		
	?9	2 470	10	F	VD	–		
	?0	2 340	10	M	VD	–		
	24	? 120	10	F	VD	–		
	3?	2 280	10	M	VD	–	Multiple pregnancy	
	32	1 540	0	F	VD	–	Multiple pregnancy	
	40	2 340	10	M	CS	–	Diabetes	

Autopsy showed heart malformation and pulmonary hyaline membranes
Autopsy showed intracranial hemorrhage and pulmonary hyaline membranes

terbutaline group and three of four infants in the control group developed HMD (Table III)

Comparing the terbutaline group with the control group there were no significant differences in maternal age (?6 2±1 0 years vs 26 8±1 6 years) birth weight (2029 0±62 5 g vs 2045 3±85 6 g) or Apgar score (7 9±0 4 vs 8 1±0 8) (Table III)

Seven infants were delivered by caesarian section) in the terbutaline treated group and of these infant developed HMD This infant was delivered in the 33rd week of gestation because of acute periappendicitis and the mother had received a total dose of 7 5 mg terbutaline intravenously during a period of 22 hours before delivery In the control group 4 infants were delivered by c s of which two developed HMD

The total material includes three neonates delivered by diabetic mothers These neonates were delivered by c s none showed any signs of HMD

Nine mothers in the terbutaline group had a cerc

Table III *Comparison of the HMD frequency gestational age birthweight and Apgar score after one minute between the terbutaline treated group and the control group*

HMD frequency	Terbutaline treated group 1/?4	Control group 5/17	Statistical significance $p<0.05$
Gestational age (weeks)	33 5±0 4	34 7±0 4	n s
Birthweight (g)			
Total	2 0 8±63 $n=24$	2 045±86 $n=17$	n s
Weeks 36–34	2 219±67 $n=11$	? 18?±70 $n=13$	n s
Weeks 33–31	1 9?2±81 $n=11$	1 600±1?5 $n=4$	n s
Weeks <31	1 575±75 $n=?$	–	–
Apgar score			
Total	7 9±0 4	8 0±0 8	n s
Weeks 36–34	8 6±0 6	8 9±0 8	n s
Weeks 33–31	7 2±0 5	5 5±1 5	n s
Weeks <31	8 0±1 0	–	–

Values are given as mean ± S E M

Table IV *Dose and route of administration of terbutaline*

Administration	Dose (mg)	Duration of treatment
Intravenously $n=8$	11± 3	26 hours±12
Orally $n=2$	236±101	32 days ±14
I v +orally $n=14$	18± 3	84 hours±13
	269± 66	19 days ± 3

Values are given as mean ± S E M

lage operation during pregnancy because of signs of cervical insufficiency earlier contsation or a known twin pregnancy According to the routine of the department all the patients with cervical cerclage were also treated with terbutaline

One infant in the terbutaline group died three days post partum due to an intrauterine infection with Listeria monocytogenes Clinical examination and autopsy showed no signs of HMD Two of the infants in the control group delivered vaginally in the 32nd week of gestation of a twin pregnancy died both within 16 and 27 hours post partum respectively Autopsy showed in both cases signs of typical HMD in one case also intracranial haemorrhage and in the other heart malformation

Indomethacin was given to three of the mothers in the terbutaline group in an attempt to prevent premature delivery (Table I)

DISCUSSION

According to the classification of beta receptors in the subgroups of $beta_1$ and $beta_2$ (9) $beta_2$ receptors are characterized to mediate uterine and bronchial relaxation and peripheral vasodilatation Selective $beta_2$ receptor stimulating drugs such as terbutaline salbutamol and ritodrine have been found to effectively decrease both frequency and amplitude of uterine contractions (1 8 11)

Studies by Kero et al (7) and Boog et al (3) indicate that antepartum administration of beta stimulating drugs such as isoxsuprine and ritodrine decreases the incidence of respiratory distress syndrome in premature infants In the study by Boog et al (3) the $beta_2$ stimulating drug ritodrine was used They found a reduced incidence of respiratory distress but the difference was only significant in infants weighing less than 2300 g However this material was not grouped according to gestational age which is an important [illegible] this context

The present study indicates that terbutaline [illegible] be effective in preventing HMD as a [illegible] reduction ($p<0.05$) of the frequency of HMD [illegible] curred in preterm infants after antepartum [illegible] tration The terbutaline and control groups are [illegible] parable with regard to factors which are reported [illegible] influence the frequency of HMD such as [illegible] age birthweight maternal age Apgar score [illegible] sex and maternal diabetes (1?) It should also be noted that compared with the control group the terbutaline group contains more infants born by [illegible] and of lower gestational age which might [illegible] that the neonates of this group should have had [illegible] greater risk of developing HMD (these differences were not significant) However the selecting the two groups differ in this study cases with advanced labour or rupture [illegible] membranes at admittance to the hospital given terbutaline

Clinical studies have demonstrated a reduced [illegible] cidence of respiratory distress in premature inf[illegible] (6 10) and an increased lecithine sphingom[illegible] ratio in amniotic fluid (4 13) after [illegible] roid administration early in the third trimest[illegible] these studies the respiratory performance of t[illegible] neonate was not observed until 24 h or more [illegible] passed following corticosteroid administra[illegible] However in many instances delivery takes pla[illegible] before any possible beneficial action of the cor[illegible] costeroid has occurred

In an experimental study (?) we have increased pulmonary distensibility after terbu[illegible] administration into fetal rabbits three hours be[illegible] preterm delivery This rapid effect of terbutal[illegible] fetal rabbit lung maturation indicates that [illegible] mechanisms than stimulation of lecithine synth[illegible] may be present A possible mechanism [illegible] might be an enhanced release of s[illegible] terial into the alveolar space as earlier s[illegible] after isoxsuprine administration to fetal rabbits [illegible] However the possibility of a dilatation of th[illegible] airways or an alteration of the pulmonary [illegible] flow in the fetuses should also be kept in mind

The mechanims behind the observed effect [illegible] terbutaline the optimal dose and the [illegible] administration are currently being studied [illegible] department

For the time being it can be sta[illegible] anterpartum terbutaline administration m[illegible]

e useful for the prevention of HMD in preterm its and that the effect of the use of beta ulating drugs always should be kept in mind n evaluating results following corticosteroid inistration

ACKNOWLEDGEMENTS

authors wish to thank Professor N Wiqvist and Ass essor I Kjellmer for reading and revising the manu pt

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Submitted for publication March 10 1977

Borrge Bergman
Dept of Obstetrics and Gynecology
Sahlgren s Hospital
S-413 45 Gothenburg
Sweden.

Acta Obstet Gynecol Scand 57 223–225 1978

MIDTRIMESTER INTRA AMINOTIC ADMINISTRATION OF PROSTAGLANDIN $F_2\alpha$ IN COMBINATION WITH AN HYPEROSMOLAR UREA SOLUTION EFFECT UPON PLASMA LEVELS OF ESTRADIOL PROGESTERONE AND HUMAN PLACENTAL LACTOGEN (HPL)

Geoffrey Sher and Maunce Katz

From the Gynecological Endocrine Service Department of Obstetrics and Gynecology University of Cape Town/Groote Schuur Hospital Cape Town South Africa

stract A study was undertaken in order to investigate clinical observation that patients who underwent ltrimester abortion using intra amniotic PG $F_2\alpha$ in nbination with hyperosmolar urea always aborted a d fetus Ten Caucasian primigravidae aged between and 22 years and whose pregnancies ranged between 14 I 23 weeks in duration were studied The patients were domly divided into two equal groups The one group eived urea and PG $F_2\alpha$ intra amniotically whereas the er received PG F α alone Blood was drawn for meas ment of plasma estradiol progesterone and human pla tal lactogen (HPL) prior to injection of the abortifa its and at regular intervals thereafter for a period of 120 . The five patients who received the combination re e of treatment (urea + PG $F_2\alpha$) showed a rapid decline he plasma concentrations of these hormones and in tion of abortion was followed by fetal death within 35 in all cases In contrast the five patients who received a-amniotic PG $F_2\alpha$ alone did not (with a single excep-) demonstrate this rapid decline in the plasma con trations of the placental hormones measured Also the same single exception these fetuses although born were alive two hours after inducing abortion

intra amniotic administration of prostaglandin in combination with hyperosmolar urea has n found to be an effective method of inducing trimester abortion (2–4 6) The advantages that method has over the use of intra amniotic staglandin $F_2\alpha$ alone outweigh the dis antages The hematologic and metabolic nges associated with the intra amniotic ad istration of prostaglandin $F_2\alpha$ in combination urea are insignificant and are no more severe when prostaglandin $F_2\alpha$ is injected alone (2 3 Moreover with the possible exception of metrial necrosis the complications associated the intra amniotic administration of pros andin $F_2\alpha$ in combination with urea do not ar to be more severe than when prostaglandin is administered alone via this route It should be borne in mind that myometrial necrosis results from the intra myometrial injection of the abortifa cients and that administration of the agents into the amniotic cavity via a correctly placed catheter will prevent the occurrence of this complication

The advantages of using the combination regime (urea + prostaglandin) rather than prostaglandin alone are as follows

(*a*) a single injection will achieve the desired re sult (2 3 6) and

(*b*) the fetus is always aborted dead This con trast with the occurrence at times of live abortuses following intra amniotic administration of prosta glandin alone (6)

In our experience the incidence of gastrointesti nal side-effects is not increased by using the combi nation regime (6)

This study was designed to measure and compare a few endocrine parameters of placental function in two matched groups of randomly selected patients The one group received prostaglandin $F_2\alpha$ alone by intra amniotic injection while the other received prostaglandin $F_2\alpha$ in combination with urea via the same route The exact time of fetal death was de termined by the disappearance of heart sounds (when this occurred within 2 hours of the first intra amniotic injection)

PATIENTS AND METHODS

Ten Caucasian primigravidae aged between 16 and ?? years whose pregnancies ranged between 14 and 23 weeks gestation were selected for this study The patients were characterized by the absence of organic disease and by the fact that without exception the indications for termination of pregnancy were psychological disturbance and/or psychiatric disease Ultrasonic investigation confirmed the clinical observation that uterine size appropriate for gestational age in each case

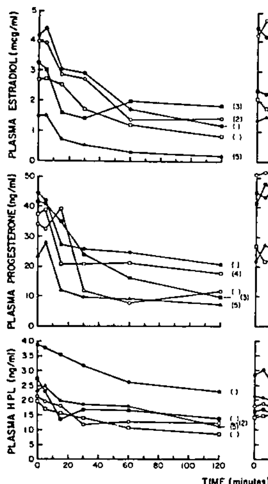


Figure 1

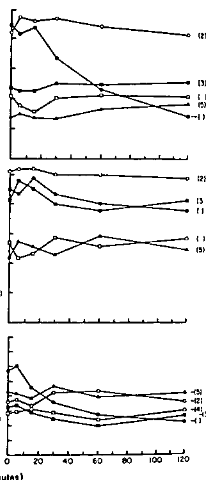


Figure 2

Fig 1 Serial plasma estradiol progesterone and HPL levels of 5 patients in Group A who received prostaglandin F_2 and hyperosmolar urea by intra amniotic injection Patient (1)=23 weeks patient (2) weeks patient (3) 16 weeks patient (4) 16 weeks patient (5) 14 weeks

Fig 2 Serial plasma estradiol progesterone and HPL levels of 5 patients in Group B who received prostaglandin F_2 alone by intra amniotic injection Patient (1)=19 weeks patient (2)=18 weeks patient (3) weeks patient (4) 14 weeks patient (5) 16 weeks

The patients were randomly divided into two groups of five each Group A received 30 mg of prostaglandin $F_2\alpha$ in combination with 100 cc of a 60% sterile urea solution by intra amniotic injection and Group B received 30 mg of prostaglandin $F_2\alpha$ alone via the same route

Blood was drawn immediately prior to the initial injection of the abortifacients and then at 5 min 15 min 30 min 60 min and 120 min following the procedure The specimens of blood were assayed for plasma estradiol progesterone and human placental lactogen (HPL) concentrations

Fetal heart sounds were recorded from the outset with a Doptone apparatus

RESULTS

Graphic illustrations of serial plasma estradiol progesterone and HPL levels are compared in Groups A and B in Figs 1 and 2

It will be noted from Figs 1 and 2 that in five cases where urea was administered in combination with prostaglandin $F_2\alpha$ via the intra amniotic route a steady decline in the plasma concentrations of the measured hormones occurred A striking difference is shown in the group of patients who received prostaglandin $F_2\alpha$ alone Four of the five patients in Group B showed no significant change in plasma estradiol progesterone or HPL levels

In all five cases constituting Group A the fetal heart became inaudible by Doptone within 35 min of injecting the prostaglandin and urea (range 19 min) In only one patient in Group B (patient did the fetus die within two hours of the intra amniotic injection of prostaglandin $F_2\alpha$ alone In this case fetal demise occurred within 3 min of injecting the prostaglandin

DISCUSSION

Numerous publications have endorsed the fact that hyperosmolar urea when administered with prostaglandin via the intra amniotic route potentiates prostaglandin induced myometrial activity (3–6) Several studies have shown that

out three hours of the intra amniotic administration of prostaglandin $F_2\alpha$ alone the peripheral plasma progesterone concentration starts to decline (5) The same studies also suggest that the rate of decline correlates well with the installation abortion interval

The evidence produced by our study corroborates the findings of Craft et al that the combination of urea and prostaglandin produces a rapid and profound decline in placental function resulting in rapid fetal demise and that the rate and degree of decline of placental endocrine function is more rapid and more constant than that which occurs following the intra amniotic administration of prostaglandin alone It is concluded that a single intra amniotic injection of urea in combination with prostaglandin $F_2\alpha$ ensures the rapid midtrimester abortion of a dead fetus (2 3 6) and as such represents an excellent alternative to the intra amniotic installation of prostaglandin $F_2\alpha$ alone

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Submitted for publication July 4 1977

Geoffrey Sher
Dept of Obstetrics and Gynecology
University of North Carolina School of Medicine
Chapel Hill N C 27514
USA

Acta Obstet Gynecol Scand 57 227–230 1978

INTRAUTERINE INJECTION OF VITAMIN K BEFORE THE DELIVERY DURING ANTICOAGULANT THERAPY OF THE MOTHER

Jørgen Falck Larsen Bo Jacobsen Hans Henrik Holm
Jan Fog Pedersen and Margit Mantoni

From the Department of Obstetrics and Gynaecology the Coagulation Laboratory and the Ultrasonic Laboratory Gentofte and Herlev University Hospitals Copenhagen Denmark

stract The coagulation factors PP^cr (Factors II+IV) tor IX and factor X were determinated in infants born mothers receiving anticoagulants The factors were ry low when the mothers did not receive vitamin K fore the delivery No significant improvement in the tors was observed after an intravenous or intraamniotic ection of vitamin K two to four days before the deliv / Vitamin K was injected intramuscularly into four tuses *in utero* using an ultrasonic multitransducer inner Three of these infants had normal coagulation tors at birth In the fourth case the factor X was normal d factor IX was significantly better than in the infants of other groups The injection had no harmful effects to infants

rombo-embolic disease is a serious complication pregnancy The incidence given by various au ors varies from 0 018 to 0 29 per 100 deliveries) Turnbull et al (17) stressed that thrombo-bolism is second only to abortion as a cause of ternal death These authors reported that during six years 1961–1966 230 women died of romboembolism associated with pregnancy in gland and Wales a fatality once in every 25 000 egnancies Two of the three maternal deaths ich occurred in Denmark during 1972 were used by thrombo-embolic disease (3)

Although postnatal maternal death from em lism has tended to decrease the incidence of tenatal embolism seems to rise (15) Therefore effective treatment for deep vein thrombosis is portant to avoid the development of pulmonary nbolism

Before the use of anticoagulants thrombo-nbolism often ended in maternal death VillaSanta 8) collected 163 case histories from the literature ith a maternal death rate of 12 8% Yahr et al (19) trodu ed the use of anticoagulants during pregnancy Since then a number of publications have confirmed that maternal death can be reduced with anticoagulant therapy (1 18)

However the anticoagulant therapy exposes the mother as well as the foetus to the hazard of haemorrhage A number of authors reported maternal complications such as postpartum haemorrhage and haematoma in the episiotomy (4 16) As these maternal complications are negligible compared with the risks of thrombo-embolic disease the major problem is foetal bleeding In a comprehensive review VillaSanta (18) found 92 cases of perinatal foetal death during anticoagulant therapy or a perinatal loss of 18 4% The anticoagulant therapy also increases the risk of brain damage in surviving infants with a diminished clotting status at birth (2)

As the use of streptokinase is contraindicated in pregnancy (15) the medical treatment of deep thrombosis leaves a choice between anti vitamin K agents such as the coumarins and indanediones and heparin The dosage of coumarins and indanediones is easy to control by an experienced doctor but the compounds pass the placental barrier They are competing with vitamin K and effect the factors II VII IX and X in the foetal blood

Severe foetal damage or even foetal death has been reported in several cases with the use of the anti vitamin K drugs Especially the use of slow acting phenprocoumone (Marcomar®) seems to expose the foetus to serious risks when controlled with long intervals (8 11)

Heparin has a molecular weight of 16 000 and it does not pass the placental barrier On the other hand the heparin treatment is difficult to maintain for a long period Heparin is only effective by injection intravenously or subcutaneously and the control of the dosage is very difficult (5)

The anticoagulant therapy may be designed as a combination of the two methods using an oral anticoagulant until 37 weeks gest ition followed by heparin until after delivery (6) This allows the foetus to eliminate the anti vitamin K drugs before delivery reducing the perinatal risk of haemorrhage

This study was undertaken to evaluate the different methods and to improve the methods by injecting vitamin K into the foetus shortly before the delivery

MATERIAL AND METHODS

The series consisted of eleven cases in which anticoagulant therapy was initiated before or during pregnancy The indications for anticoagulant therapy were thrombo embolic disease or—in one case—a Key-Shiley prosthesis The women received treatment with phenindione by mouth until one or two weeks before the expected time of delivery Then the anti vitamin K treatment was replaced by intravenous heparin The phenindione treatment was controlled by frequent estimations of the Owen PP% (Factors II+VII) while the factors IX and X were screened at longer intervals

After the termination of anti vitamin K treatment and the initiation of heparin injections different procedures were evaluated

Group I In the first part of this study it was decided to perform a caesarean section in two cases assuming that this mode of delivery would be less traumatic for the foetus than a vaginal delivery These mothers did not receive vitamin K before the delivery

Group II Three mothers were given large doses of vitamin K (10–30 mg) intravenously between two and four days before the delivery As vitamin K crosses the placental barrier it was expected to correct the coagulation status

Group III In two cases the vitamin K was injected into the amniotic fluid In the first case 10 mg were injected days before the delivery In the second case 30 mg injected four days before the delivery

Group IV In four cases the foetus was given an intramuscular injection of 2 5–3 0 mg phytomenandion *in utero*

A locally constructed ultrasonic multitransducer scanner was used (10) It operates with an array of 50 transducer units which are activated sequentially The system yields real time cross sectional images of a 10 cm wide and 16 cm deep area consisting of 50 parallel lines Through a special puncture adapter which can be fastened to one end of the transducer it is possible to introduce and manipulate a needle in the rectangular sound field (7)

Initially the buttocks of the foetus were located Then under sterile conditions a guide needle 1 2 mm o d was passed via the puncture adapter through the abdominal and uterine walls aiming at the buttock As the needle entered the sound field it became visible on the real time cross sectional scanning picture Through the guide needle a long 0 6 mm o d needle was inserted into the uterine cavity where the tip of the needle could be seen. V under direct monitoring the thin needle was adva into the buttock of the foetus and the phytomenand was injected

Before the intrauterine injection the mother receiv mg vitamin K intravenously Immediately after the inj tion of phytomenandion the anticoagulant therapy continued using intravenous heparin The heparin given by infusion controlled by the trombin time prothrombin time a m Quick and plasma recalcificat time The infusion of heparin was stopped few hours fore delivery

Immediately after the delivery the phenindione tre ment was resumed by an injection of 200 mg phenindione followed by medication by mouth

The newborn infant received 5 mg phytomenandion in tramuscularly as soon as blood was obtained for coag tion analyses

Coagulation status on the new born infants

The analyses were carried out on blood from the umb cord or—in two cases—from the scalp vein

Factors II and VII were determined by the meth Owren & Aas (9) *Factor IX by the method of Rod al (13) and the factor X according to Sise et al (14)*

CASE HISTORIES

Case 1 A B W 30 years old gravida III para II admitted to the hospital because of vaginal bleedi g dur the 17th week of pregnancy Few days after the admiss the patient developed a *profound pelvic thrombosis* c firmed by phlebography (only a single picture was tak Oral anticoagulant therapy was started using phenind When the expected time of delivery was reache *L/S* ratio was determined *The L/S ratio was* 2 5 and estimated foetal weight was 2 700 g The foetus was gi 3 mg phytomenandion intramuscularly Two days lat labour was induced using a Cardiff infusion instrume The mother was given 1 mg *phytomenandion* and anticoagulant therapy was reestablished using hep The patient was delivered of a normal girl 2 750 g A score 9/9 After the delivery the oral anticoagulant the was started again

Case 2 E N 30 years old gravida IV para III was admitted to the hospital during the 26th wee pregnancy with an ilio femoral popliteal thrombosis T weeks before the estimated *time of delivery* the fo weight was judged to 3 000 g and the L/S ratio was 3 5 mg phytomenandion was injected in o th foetus an anticoagulant therapy was changed from phenindion heparin The labour was induced two days later and normal girl was born 3 150 g Apgar score 10/10

Case 3 M L 24 years old gravida II para I admitted to the hospital in the 20th week of pregn with an a ute abdomen *Appendicectomy* was perfo but the appendix was normal Four days later the pat had a pulmonary embolism and anticoagulant therapy initiated Two weeks before the expected time of del the L/S ratio was 3 2 and the foetal weight was estim to be more than 2 500 g 2 5 mg phytomenandion

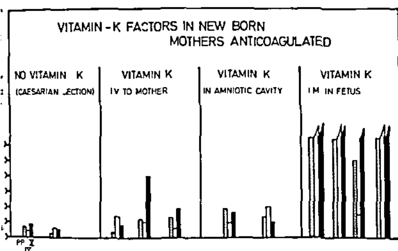


Fig 1 Coagulation factors in eleven infants born by mothers treated with anticoagulants For each infant the values are indicated with three columns as percent of normal adult values First column I P% Second column factor IX Third column Factor X

jected intramuscularly in the foetus The mother was kept on a heparin infusion until the delivery 30 hours later A normal boy ?800 g was born the Apgar score 10 and the infant did not have any sign of haemorrhagic complications

Case 4 K D H 25 years old primigravida was admitted during the fourth month of pregnancy because of a profound thrombosis of the left leg Oral anticoagulant therapy was initiated Two weeks before expected time of delivery the foetal weight was estimated to 3 400 g The foetus received ? 5 mg phytomenandion intramuscularly The mother was given vitamin K intravenously and the anticoagulant therapy was continued with heparin One day later labour was induced with oxytocin During the second stage of labour serious decelerations in the cardiotocogram forced the obstetrician to apply a vacuum extractor The patient was delivered of a healthy boy 36 hours after the injection of vitamin K 3 600 g Apgar score 10 There was no sign of intracerebral haemorrhage

RESULTS

All eleven mothers and their infants survived One of the mothers who was delivered by caesarean section developed a pulmonary embolism but recovered

Fig 1 illustrates the results of the coagulation analyses All the coagulation factors were extremely low in the group in which the mothers did not receive vitamin K Phytomenandion given to the mother a few days before the delivery did not improve the coagulation status significantly except the factor X in one of the cases Intraamniotic injection of vitamin K few days before the delivery had the same unsatisfactory effect

Intramuscular injection of vitamin K into the foetus *in utero* resulted in coagulation factors within the normal (adult) range in three of the four infants In case 3 the factors were significantly better than in the infants of the other groups The factor X was normal but the PP% and factor IX were still reduced

The injection marks were found in the gluteal region of the infants of group IV and the injections had caused no harmful effects

DISCUSSION

The coagulation status of the infants of group I in which the mothers did not receive vitamin K before delivery confirms the assumption that the oral anticoagulant has passed the placental barrier The infant is exposed to great risk of haemorrhage during the delivery even in case of caesarean section

Injection of vitamin K to the mother (group II) did not improve the coagulation status for the newborn Hirsh et al (6) introduced this method Pridmore et al (12) treated 15 mothers with 5 mg of vitamin K seven to ten days before induction of labour All the infants were normal and healthy and in the 12 tested the cord prothrombin times were within the normal range However the prothrombin time or prothrombin ratio is not suitable for the estimation of the vitamin K factors It is not influenced by variations in factor IX and very little sensitive to factor X Furthermore the slightest contamination of gelatinous tissue from the umbilical cord alters the thromboplastin time significantly In our study the factors II VII IX and X were studied and they were all very low

Based on the literature and their own investiga-

tion Pridmore et al (12) suggest that the minimum time necessary for the effect of oral anticoagulants on the foetus to wear off is somewhere between three and fourteen days In our study the longest time interval between the injection of vitamin K to the mother and the delivery was four days This may explain why the coagulation status in these infants did not improve

Injection of vitamin K into the amniotic fluid did not give any better results In these cases the longest time interval between the injection and the delivery was four days also Again the time may be too short to allow the foetus to resume a normal coagulation status

The coagulation status of three of the infants *which received an intramuscular injection of vitamin K in utero* was normal In only one case were the values subnormal In that case the delivery took place 30 hours after the injection of vitamin K to the foetus Therefore the time interval may have been too short However the coagulation status was even in this case better than in the infants of the other groups

It is possible that injection of vitamin K into the mother seven to ten days before the delivery may give as good results as the presented method of injecting the vitamin K into the foetus However the administration of heparin is difficult and it is an advantage if the heparin treatment can be reduced to 48 hours Using the L/S ratio the optimal time of induction of labour may be determined The vitamin K can be given as soon as the *L/S* ratio is higher than 2 0 and the oral anticoagulant should be replaced by heparin Labour can then be induced 48 ours later

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Submitted for publication Nov 18 1976

Jorgen Falck Larsen
Department of Obstetrics and Gynaecology
Herlev University Hospital
DK 2730 Herlev Copenhagen
Denmark

Acta Obstet Gynecol Scand 57 231–235 1978

CHANGES IN FETAL SUPRAVENTRICULAR EXTRASYSTOLES DURING UTERINE CONTRACTIONS IN LABOUR

Helge Jenssen

From the Department of Obstetrics and Gynecology
Aker Hospital (Oslo City Hospitals) Oslo Norway

bstract The electrocardiogram and phonocardiogram were recorded from a fetus exhibiting supraventricular ectopic beats during labour The ectopic beats showed increased amplitude of the first heart sound (S_1) compared to sinus and postectopic beats the R–S_1 interval was prolonged and the mechanical systole measured as the S_1–S_2 interval shortened During uterine contractions these parameters were measured every 10 sec The S amplitude of the ectopic beats decreased simultaneously the R–S interval increased and the S_1–S_2 interval shortened The changes were delayed compared to the amniotic pressure curve The changes found can be explained by a shift of blood between the fetus and placenta caused by uterine contraction

Conspicuous changes related to uterine contractions were observed in the fetal phonocardiogram (FPCG) in a recording made during labour in which the fetal heart showed supraventricular ectopic beats (Fig 1) An analysis of the FPCG and the simultaneously recorded fetal electrocardiogram (FECG) was undertaken measuring systolic time intervals (5) The arterial pulse was not recorded

CASE STUDY

The mother was 28 years old and gravida II One and a half years earlier she had delivered a stillborn fetus in the 38th week She was admitted in the 36th week because of arterial hypertension RR 140/100 Estriol excretion varied between 12 and 24 mg per 24 hours Blood pressure fell to normal values within 24 hours but she was kept in the ward for nearly 2 weeks chiefly due to anxiety caused by the previous stillbirth

Four days after expected term she was readmitted without signs of preeclampsia in active labour and had an uneventful spontaneous delivery after 7 hours of contraction The newborn a boy scored Apgar 8/10 at 1/5 min of age and weighed 3 630 g On the first day of life a pediatrician found some extrasystoles but no other pathological findings Three days later no extrasystoles were detected An ECG of the newborn showed normal P waves and no extrasystoles Several routine examinations by another pediatrician up to the age of 1 year showed normal development The placenta was normal macroscopically and weighed 500 g

METHOD

The FECG and FPCG were recorded during first stage of labour at a cervical diameter of 4–5 cm Two hours earlier the mother had received diazepam (Stesolid "Dumex"®) i m During contractions she was hyperventilating to some degree breathing N_2O/O_2 50/50% through an open mask Amniotic pressure was registered as earlier described (7) The FECG was registered with a scalp spiral electrode the signal was passed through a pre amplifier (EMT 1 [1]) The FPCG was recorded from the maternal abdomen with a heart sound microphone (EMT 25 B) and passed through a band pass filter with a nominal setting of 50 Hz and a pre amplifier (EMT 22) The signals were written on a Mingograph 34 continuously during the contractions paper speed 100 mm/s Measurements were made every 10 sec (s) starting 40 s before peak contraction pressure (Fig 2)

The parameters measured are given in Table I As the Q wave varied to some extent R–S interval was measured

Table I *Characteristics of sinus beats ectopic beats and postectopic beats Mean values between uterine contractions*

R–R time between the R waves of the actual and preceding beats S_1 first heart sound S_2 second heart sound

		Sinus beats	Ectopic beats	Postectopic beats
R–R interval	ms	4 2	795	5_5
S_1–S_2 interval	ms	205	167	205
S_2–S interval	ms	270	90*	370*
R–S interval	ms	36	45	30
S duration	ms	75	75	84
S duration	ms	63	60	53
S amplitude	mm	11	23	8
S amplitude	mm	9	11	6

From S_2 of the preceding sinus beat to S_1 of the ectopic beat
* From S_2 of the ectopic beat to S of the postectopic beat

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[1] Manufacturer Elema Schönander Stockholm

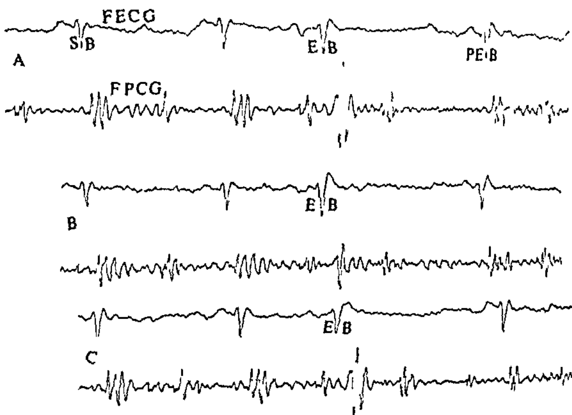


Fig 1 Fetal electrocardiogram (*FECG*) and phonocardiogram (*FPCG*) recorded simultaneously *A* before uterine contraction *B* 10 seconds after maximal amniotic pressure (peak contraction pressure) and *C* 40 seconds after *B* *SB* sinus beats *EB* ectopic beats *PEB* postectopic beats The FECG was registered with downward deflection of the *R* wave

instead of Q–S_1 interval The start of S_1 and S_2 was defined as the crossing point between the first high frequency vibration and the base line level Using a magnifying lens and the smallest marks on the Mingograph paper readings were made to the nearest 2 5 millisec (ms) Each value was the mean of 2–5 individual readings and the values presented are the means of 2 consecutive contractions

RESULTS

Between uterine contractions

The FECG trace was inverted (Fig 1) However between contractions the *P* waves were well delineated The *PQ* time of the sinus beats was 60 ms of the ectopic beats 80–85 ms and of the postectopic beats 60 ms

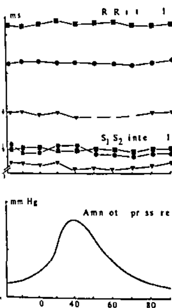
The amplitude of S_1 and S_2 was increased in the ectopic beats the S_1–S_2 interval was shortened and the R–S_1 interval prolonged (Table I) If the time of isovolumetric relaxation of the ventricles is disregarded the S_2–S_1 interval may be taken as a measure of ventricular filling time The S_2–S_1 in end [illegible] preceding the ectopic beats is 41 % and that preced[illegible] ing the postectopic beats 168 % of the sinus beats

During uterine contractions

Fetal heart rate measured as the R–R interval d[illegible] not vary during contractions (Fig 2) The S_1–S[illegible] interval of the ectopic beats shortened at peak con[illegible] traction pressure the shortening being maximal ([illegible] ms) 20 s later and lasting 30–35 s

The S_1 amplitude of the ectopic beats decrease[illegible] 37 % and of the sinus beats 19 % during contractions (Figs 1 and 3) These changes too were dela[illegible] compared to the peak contraction pressure The S[illegible] amplitude changed as shown in Fig 4

The duration of the R–S_1 intervals in the e[illegible] beats (but not in the sinus or postectopic beats [illegible] increased during uterine contractions (Fig 4) [illegible] increase starting at the time of peak co[illegible] pressure being maximal (27 %) 10 s later and la[illegible] 35–40 s



2 Mean of R–R interval and S_1–S_2 interval measured ry 10 sec shown in relation to the amniotic pressure ve ●—● sinus beats ▼—▼ ectopic beats ■—■ tectopic beats ms milliseconds s seconds

The duration of S_2 of the sinus and ectopic beats s 25% shortened simultaneously with the nges in S_1 amplitude and R–S_1 interval The ation of S_2 of the postectopic beats did not rten

DISCUSSION

fetal ectopic beats resemble the supraventricu extrasystoles of the human adult in its altered P e configuration increased S_1 amplitude and longed R–S_1 interval (2) The compensatory se was not complete and the ventricular com t of the ectopic beats was virtually unchanged ectopic beats of the present case is considered ave a supraventricular origin

he duration of R–S_1 and S_1–S_2 intervals of the is beats are the same as reported by others (3

he pressure increase during uterine contraction o small to influence the velocity of propagation he fetal heart sounds to a measurable extent

he R–S_1 interval of the ectopic beats increases peak contraction pressure simultaneously S_1 plitude decreases Disappearance of the initial deflection of S_1 accompanying decrease of amplitude cannot explain the R–S_1 interval change as the duration of S_1 did not change The sum of R–S_1 and S_1 duration increased during contraction in the same manner as the R–S_1 interval

The delay of S_1 in the ectopic beats is accompanied by delay in central arterial pressure increase in systole (14) and may be partly caused by the increased aortic pressure at the start of the ectopic beats If the duration of the S_2–S_1 interval preceding the ectopic beats is applied to the aortic pressure curve recorded in the newborn (13) aortic pressure at the start of the ectopic beats systole is still about 35% of maximal aortic pressure In hypertensive adults prolonged Q–S_1 intervals have been found (15)

Among causes of a loud first heart sound Leatham lists reduced ventricular filling from atrioventricular stenosis or tachycardia (9) In dogs Sakamoto et al (11) showed that among several factors influencing S_1 amplitude the only common factor was the rate of left ventricular pressure increase a rapid pressure increase giving a high S_1 amplitude Decreased ventricular filling in the ectopic beats therefore explains the high S_1 amplitude

Shortening of the S_1–S_2 interval in the ectopic beats may be caused by increased aortic pressure or reduced cardiac filling

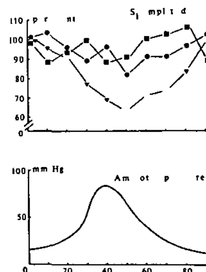


Fig 3 Relative changes of S_1 amplitude related to uterine contraction Symbols as in Fig 2 The values of Table I taken as 100%

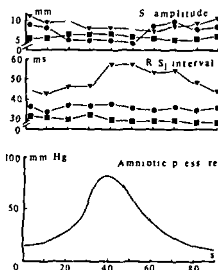


Fig 4 Changes of S_2 amplitude and R–S_1 interval duration related to uterine contraction Symbols as in Fig 2

During uterine contraction the intervillous circulation is partly or totally stopped (1) Peak contraction pressure of the contractions studied was 60 to 70 mmHg probably occluding intervillous circulation *During amniotic pressure rise there must be a* period of intervillous space increase as the veins draining the intervillous space are occluded before the arteries

The intervillous space increase may have an effect on the fetal circulation A bolus of blood may be squeezed from the placenta to the fetus temporarily increasing the return of blood to the fetal heart Resistance in the chorionic tree may increase causing elevation of the fetal arterial pressure *These circulatory changes may explain the* principal variations during uterine contraction found in the present case (change of the S_1 amplitude and the R–S_1 and S_1–S_2 intervals)

A 10% reduction of newborn s predicted total blood volume during exchange transfusion (4) did not alter the R–S_1 interval but significantly shortened the R–S_2 interval and consequently the S_1–S_2 interval However exact timing of S_1 was inaccurate due to small amplitude

Khanna et al (8) reduced stroke index in adults with peripheral cuffs This procedure prolonged the pre ejection period and shortened left ventricular ejection time Presuming that the R–S_1 interval partially reflects pre ejection period changes (6) and that the S_1–S_2 interval reflects changes of left ventricular ejection time (5) the changes related to uterine contractions are mainly caused by cl in return of blood from the placenta

The present case shows that the fetal s time intervals has the ability to change mucl the adult and that the changes are measurabl findings add support to the hypothesis that a blood between the fetus and placenta takes during uterine contraction

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Submitted for publication March 3 1977

Helge Jenssen
Department of Obstetrics and Gynecology
Aker Hospital
Oslo
Norge

Acta Obstet Gynecol Scand 57 237–240 1978

THERAPEUTIC ABORTION

The 1975 report from Ulleval Hospital

Fritjof Jerve and Petter Fylling

From the Department of Obstetrics and Gynecology Ulleval Hospital Oslo Norway

stract The results from a prospe tive study of 1228 rapeutic abortions (the 1975 material) are reported st trimester pregnancies (1028 cases) were terminated suction and curettage and second trimester pregnancies prostaglandins (200 cases) The overall follow-up (4–6 eks after termination) was 94 3% The incidence of rforation was 0 5% of the surgical terminations none of uch however resulted in any other complications The an incidence of re admission was 3 9% the main uses being retained products or pelvic infection The an incidence of pelvic infection (salpingitis/ rametritis) was 1 6% The highest incidence of pel infection was found in early pregnancies (≤8 weeks) nulliparous women (7 7%) and the lowest (1 5%) the induction group

rgi al complications associated with therapeutic ortion have gradually decreased during the last cade This trend is concurrent with the increase the number of therapeutic abortions performed provement of the techniques and greater experi e and training of medical personnel in this spe l field (2 11 13 18 19 22 23) Hence prospec studies for limited periods and a certain nogeneity of the staff involved should give a re reliable picture of the current situation in each itre or region

Our 1975 material on therapeutic abortion based recording each step of the treatment procedure EDB forms specially designed for this purpose eviewed

MATERIAL AND METHODS

series consists of 1 228 pregnancies that were termi ed at our clinic in 1975 All women underwent aecological examination at our outpatient clinic 1–7 s prior to the termination The majority of the women e examined by one of us (P F) At this initial visit the dical history was recorded and the size of the uterus imated Samples for the relevant laboratory tests such Rh etc were also secured at this visit

Based on the size of the uterus the women were divided into 2 groups The first group included nulliparous women ≤11 weeks pregnant and parous women ≤12 weeks preg nant The second group included all second trimester pregnancies and also nulliparous women 12 weeks preg nant The first group was treated on an outpatient basis by a surgical method A few patients in this group were admit ted to hospital for simultaneous sterilization or because of pregnancies complicated with medical disorders such as diabetes etc The second trimester pregnancies were ter minated by induction

Surgical procedure The women attended the outpatient clinic in fasting condition at 8 o clock a m and the termi nations were performed under i v anaesthesia by cervical dilation and vacuum aspiration As a general rule a vacu um metal aspiration curette No 8 was used up to 9–10 weeks and No 10 after 9–10 weeks The women were observed 3–4 hours postoperatively and then discharged from the hospital

Induction of abortion All inductions were performed by prostaglandins Different methods were used as parts of clinical trials administered by the Prostaglandin Task Force Karolinska Institutet Stockholm

Eighteen women underwent sterilization simultane ously with the termination (4 by laparotomy and 14 by laparoscopy)

Vaginal bacteriological screening was not performed as a routine No pregnancies were terminated by hysterotomy and Gammaglobulin was given to all Rh negative women

Follow-up On discharge from the hospital all women were given an appointment for a follow-up visit and writ ten instructions which emphasized the importance of con trol If a woman failed to keep this appointment about 4 weeks later she received a new one by mail If she still did not appear she was given a third chance by filling in a questionnaire which was sent to her by mail

The data recorded were handled by the municipal EDB-department

RESULTS

The distribution of the material according to age groups is illustrated in Fig 1 As many as 24 2% of

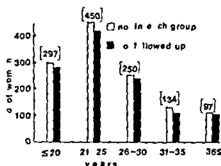


Fig 1 Distribution of the material in age groups The total number in each group is indicated in the parentheses

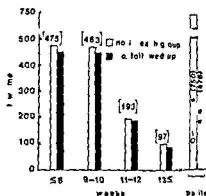


Fig 2 Distribution of the material in gestational length and parity The total number in each group is indicated in the parentheses

the women were less than 21 years old and 36 4% were between 21 and 25 years old

As shown in Fig 2 the majority of the pregnancies (76 4%) were terminated within the first 10 weeks of gestation and 61 1% of the women were nulliparous

The main peroperative complications are listed in Table I but none of them were serious None of the 5 uterine perforations i e 0 5 per cent of the surgical terminations resulted in any other immediate or late (4–6 weeks) complications Patients with uterine perforations were observed in the hospital overnight and then discharged Although the figures are small they might indicate a certain percentage increase in the incidence of perforations with increasing gestational length

As may be expected a higher incidence of cervical laceration was observed in the nulliparous group However the lacerations were always of minor degree and did not necessitate any treatment The bleeding recorded in 12 patients was also of moderate degree and blood transfusion was given in only one case a prostaglandininduced abortion

Fig 3 shows the incidence of re admission or pelvic infection related to age groups or parity By far the highest incidences of both re admission and pelvic infection were found among young (≤ years) or nulliparous women

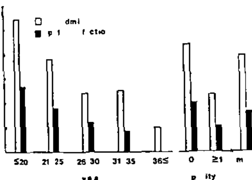
Fig 4 illustrates the incidence of re admission pelvic infection related to gestational length methods used Contrary to what was expected the percentage highest incidence of pelvic infection found in the ≤8 weeks group while in the induction group (200 cases) only 3 cases were observed These 3 cases were nulliparous women and one of them was 12 weeks and the 2 others were 13 weeks pregnant

The percentage re admission seems to be a fairly good indicator of the quality of the technical procedure In Table II the percentage of re admission related to the different medical officers is illustrated The clinical and technical experience of the medical officers A–C was greatest and that of G–I was least Bleeding pain or fever were the most common symptoms causing re admission

Follow up 1 108 or 90 2% of the women appeared at the follow up visit and 50 replied to questionnaires Hence we obtained postoperative information on totally 94 3% of the material The postoperative period varied from 4 to 8 weeks mostly 4 to 5 weeks

Table I *Peroperative complications related to gestational length or parity*

	Gestational length in weeks				Parity		Total
	≤8	9–10	11–12	13≤	0-Parous	Parous	
Perforation	3 (0 6%)	1 (0 2%)	1 (1 0%)	0	4 (0 6%)	1 (0 [illegible]%)	5 (0 [illegible]
Laceration of the cervix	1 (0 2%)	1 (0 2%)	0	1 (1 0%)	3 (0 4%)	0	3 (0 [illegible]
Bleeding	2 (0 4%)	3 (0 6%)	5 (2 6%)	0	5 (0 7%)	5 (1 0%)	10 (0 [illegible]



3 The incidence of re admission or pelvic infection (salpingitis/parametritis) related to age groups or parity

DISCUSSION

The present material is similar to some previous reports concerning age and parity (3 15 19 23)

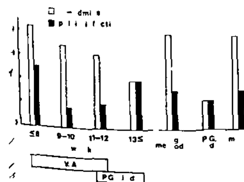
Intravenous administration of Brietal Natrium® ... was found to be a very suitable anesthesia for this type of surgery We recorded a low percentage of discomfort among patients shortly after the procedure Although we are aware of the widespread use of local anesthesia for this type of surgery (1 9 15 19) at least in our hands i v anesthesia seems to be preferable because of the anxiety for the procedure usually experienced by women in our population

We found relatively few perioperative complications in the present material The figures for perforation (0 5%) are higher than those reported by some others (6 9 12 16 17 19) but none of the perforations caused any additional damage Three out of the 5 perforations occurred in cases of early pregnancy (≤8 weeks) It is reasonable to assume that this complication at least in the 8 weeks group could be avoided by using Karman cannulae (10 15) On the other hand a higher incidence of retained products is reported using plastic cannulae compared with metal ones (3)

Exact quantitation of peroperative bleeding was not performed in the present series Bleeding more than usual was recorded as bleeding In only one case a second trimester abortion induced by prostaglandins the bleeding necessitated a blood transfusion

Other peroperative complications were also relatively few especially in the second trimester group compared with some previous reports (2 6–8 11 13 19 22 23) As already reported by several investigators reviewed by Brenner (4) induction of second trimester abortion by prostaglandins is superior to other methods for termination Hence surgical termination of pregnancies beyond the 12th week should be avoided However the intermediate group (10–11 weeks) might still be terminated by vacuum aspiration eventually combined with preoperative prostaglandin treatment

The figures for post termination complications will obviously be dependent on 1) the criteria used in the assessment of complications 2) the evaluation techniques used and 3) the observation period The highest incidence of salpingitis/parametritis was observed in the ≤8 weeks group and this was entirely unexpected At least 3 possibilities exist (*a*) it is more difficult to empty the cavity completely in this group (*b*) the medical officer may consider the procedure to be easier in this group and hence might not be vigilant enough during the vacuum aspiration procedure (*c*) some factors like high sexual activity causing a higher prevalence of pelvic infections in this group Of a total of 20 cases with pelvic infection in the ≤8 group as many as 17 were nulliparous Hence in the authors opinion a combination of causes is a reasonable explanation



4 The incidence of re admission or pelvic infection (salpingitis/parametritis) related to gestational length and methods used V A = vacuum aspirations P G = prostaglandin induced abortions

Table II *Percentage re admission per medical officer*

Medical officer	A	B	C	D	E	F	G	H	I
Re admission	3 0	3 2	3 3	4 0	4 2	4 7	4 8	5 0	5 9

for the higher incidence of pelvic infection in early pregnancy

The policy has been to terminate the pregnancies as early as possible as this has proved beneficial both from a psychological and somatic point of view (14 19 20) Since the present methods for terminating early pregnancies at least in our hands do not appear to be so satisfactory as anticipated greater efforts must now be made to improve these procedures

ACKNOWLEDGEMENT

This investigation received financial support from the World Health Organization

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Submitted for publication Febr 16 1977

Fritjof Jerve
Department of Obstetrics and Gynecology
Ullevål Hospital
Oslo
Norway

Acta Obstet Gynecol Scand 57 241–244 1978

EFFECT OF FASTING ON BLOOD GLUCOSE OF PARTURIENT AND HER FULL TERM INFANT

R S Ikonen E Hagman and P Pystynen

From the Departments of Paediatrics and Obstetrics and Gynaecology Central Hospital of Tampere and the Institute of Clinical Sciences University of Tampere Tampere Finland

tract The series consists of 100 parturients and their term infants According to the fasting time of the urients before delivery the series was divided into e groups Group I fasting from 6 to 12 hours (49) up II from 12 to 18 hours (38) and Group III over 18 rs (13 parturients) The blood glucose level of the hers was examined immediately after delivery and of their infants at birth and at the age of two and six rs There were no significant differences between the an blood glucose level of the mothers in different fast groups 5 0±0 8 mmol/l in Groups I and II and ±0 9 mmol/l in Group III There was a significant tive correlation between the blood glucose level of nts at birth and that of their mothers (r 0 44 p<0 001) e blood glucose level of the infants at the age of two and hours did not correlate to that of their mothers Blood cose of the infants was lowest at the age of two hours an 2 5±0 6 mmol/l) and there was no significant dif ence between the groups at any age Hypoglycaemia od glucose less than 1 7 mmol/l) was found in 15 cases %) Four were treated because of symptomatic oglycaemia

olonged fasting of parturients during labor and ivery is not unusual We decided to investigate ting in labour when we noticed that many in ts had very low blood glucose values soon after th In our hospital women were given no food d only water to drink when they were in active our

ble I *Fasting groups*

oups of rturients	No of par turients	Fasting time (h) (mean ± 1 S D)
oup I (6–12 hours)	49	9 4±2 5
oup II (12 18 hours)	38	14 6±1 3
oup III (over 18 hours)	13	19 7±1 5

MATERIAL AND METHODS

The study consists of 100 parturients who delivered normally at term The parturients were divided into three groups according to the fasting time before delivery (Table I) Group I fasting time from 6 to 12 hours (49 parturients) Group II fasting time from 12 to 18 hours (38 parturients) and Group III fasting time over 18 hours (13 parturients) By the term fasting time was understood the interval between the last meal (according to information obtained from the parturients) and the delivery

The blood glucose level of the mothers was estimated by taking a capillary blood sample immediately after delivery and that of the infants at birth and at the age of two and six hours Blood glucose was determined by glucose oxidase method (Kabi Technicon Auto Analyzer II) The infants were given 5% glucose at the age of two hours and thereafter were breast fed six hourly with additional glucose when necessary

There was no significant difference between the groups in infants gestation age birth weight and condition at birth as estimated by one minute Apgar Scoring (Table II) The mean gestation age was slightly over 40 weeks birth weight about 3 500 g and Apgar score 8 8

RESULTS

There was no significant difference between the mean blood glucose level of the mothers in different

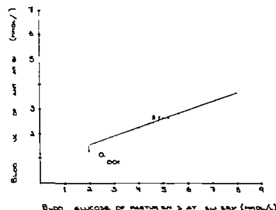


Fig 1 Correlation between blood glucose of infants at birth and parturients at delivery

Table II *Gestation age birth weight and 1 min Apgar score distribution of infants in the different groups*

Fasting groups	Gestation age (weeks) (mean ±1 S D)	Birth weight (g) (mean ±1 S D)	1 min Apgar score (mean ±1 S D)
Group I	40 4±1 3	3 610±520	8 9±0 6
Group II	40 2±1 4	3 540±480	8 8±0 7
Group III	40 1±1 0	3 410±370	8 8±0 7

Table III *Blood glucose of parturients at delivery and infants at birth and at two and six hours age*
In parentheses the number of cases in which blood glucose was not estimated

Fasting groups	Blood glucose of parturients (mmol/l) (mean ±1 S D)	Blood glucose of infants (mmol/l)		
		At birth	Aged 2 h	Aged 6 h
Group I	5 0±0 8 (1)	2 5±0 6	2 5±0 5 (7)	2 8±0 6 (9)
Group II	5 0±0 8 (2)	2 6±0 7 (1)	2 5±0 6	2 7±0 5 (4)
Group III	5 2±0 9	2 7±0 5	2 3±0 5	2 8±0 5 (1)

Table IV *Incidence of hypoglycaemia in infants (blood glucose less than 1 7 mmol/l)*

At birth	Aged 2 h	Aged 6 h	All
6	7		13
1	1		1
	1	1	1
Treated because of hypoglycaemia			4

Table V *Blood glucose of hypoglycaemic infants compared to that of their mothers at delivery*
Blood glucose (mmol/l)

Infants at birth	Their mothers	Infants aged 2 h	Their mothers
1 6	5 6	1 6	5 6
1 6	5 2	1 6	5 2
1 5	4 0	1 6	4 8
1 4	4 7	1 6	4 6
1 2	3 8	1 4	6 0
1 2	3 8	1 4	5 6
1 2	–	1 4	5 2
		1 3	6 3
		1 0	5 4

fasting groups (Table III) 5 0±0 8 mmol/l in Groups I and II and 5 2±0 9 mmol/l in Group III These values are quite high but within the normal range for adults

No significant difference was also found between the mean blood glucose level of the infants in Groups I II and III at any age The mean blood glucose was lowest at the age of two hours (2 5 mmol/l)

Although there was no difference between the blood glucose values in various fasting groups there was a statistically significant positive correlation between the blood glucose of infants at birth and that of their mothers at delivery (Fig 1)

The blood glucose level of the infants at the age of two and six hours did not correlate with that of their mothers (Figs 2 and 3)

The incidence of hypoglycaemic values in the

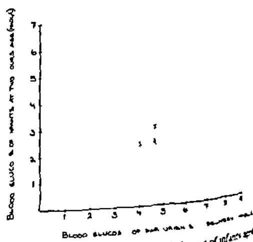


Fig 2 Correlation between blood glucose of infants aged 2 h and parturients at delivery

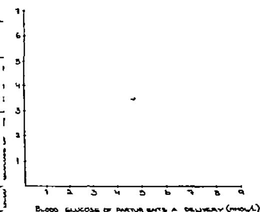


Fig 3 Correlation between blood glucose of infants aged h and parturients at delivery

ormally delivered full term infants was 15% (Table V) Blood glucose below 1 7 mmol/l was consid red hypoglycaemic In seven cases there was a ypoglycaemic value at birth and in eight cases at he age of two hours In one case there was a ypoglycaemic value both at birth and at the age of wo hours and in one case at the age of two and six ours Four infants were treated because of symp omatic hypoglycaemia

When comparing the blood glucose level of ypoglycaemic infants to those of their mothers here was found a correlation between the blood lucose of the infants at birth and that of their nothers at delivery but not later (Table V)

DISCUSSION

n earlier investigations (1 9) it has been shown that lood glucose of the fetus and the newborn at birth orrelates with blood glucose of the mother and hat maternal hypoglycaemia can cause fetal ypoglycaemia (8) It has also been postulated that lood glucose values of parturients vary depending with the time of the last meal (3) In contrast in this tudy there was no correlation between the fasting ime of parturients and their blood glucose level and that of their newborn infants The explanation of this may be increased corticosteroid production caused by the stress of labor and delivery to the parturient

Blood glucose of infants was lowest at the age of two hours which is in agreement with earlier studies (3 7) Cornblath et al (2) have reported in appropriate for gestational age infants blood sugar values of less than 30 mg/100 ml in 13 7% of the cases during the first six hours In Lubchenco & Bard s series (6) the incidence of blood sugar values of less than 30 mg/100 ml was 11 4% in a general nursery population before the first feedings at six hours of age In this study hypoglycaemic values (blood glucose less than 1 7 mmol/l which corresponds 30 mg/100 ml occurred in 15% of the cases during the first two hours and was present in half of the babies at birth Later there was no new cases of hypoglycaemia perhaps because of early feeding

The concept of hypoglycaemia in the newborn has changed in recent years and the classification has been revised (4) The greatest incidence of hypoglycaemia has been found to be immediately after birth (4) as in this study Perinatal asphyxia is possibly one important factor in its development (4 5 6) In this study the infants were born in good condition but even then the incidence of low blood glucose values was 15% In most the situation was corrected without any special management With babies at risk screening of blood glucose should be initiated during the first hours after birth and early feeding used to prevent hypoglycaemia

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Submitted for publication March 12 1977

R S Ikonen
Department of Paediatrics
Central Hospital of Tampere
33520 Tampere 52
Finland

Acta Obstet Gynecol Scand 57 245–248 1978

CAESAREAN SECTION

A clinical study with special reference to the increasing section rate

Eva Patek and Bertil Larsson

From the Department of Obstetrics and Gynecology Huddinge Hospital Huddinge Sweden

bstract At Huddinge University Hospital 539 Caesarean ctions (C S) were made among 8415 deliveries from ctober 197? to June 1976 corresponding to an over all S rate of 6 4% Over these years the rate has increased om 3.5% in 1972 to 9 7% in 1976 The main increase was ie to a higher incidence of abdominal deliveries in cases imminent fetal asphyxia The maternal complication te and the neonatal morbidity rate were both 6 5 times gher and the neonatal mortality rate was 4 1 times higher emergency than in elective surgery There was neither ly mortality nor any morbidity in infants delivered by ective C S from healthy mothers at term

ecently an increased rate of C S was reported not ly in Sweden but also in USA and West ermany (5–7) With the growing emphasis on the itenatal and intrapartum status of the fetus and ith the addition of laboratory tests and technical ogress of internal fetal monitoring an increased te of C S should be expected (1) However there ust be an optimal rate of C S in which the mater al risks are in balance with the benefits of the tus-child In a recent paper it was pointed out that S should still be regarded as the most dangerous ay of delivery not only for the mother but also for e child (7)

The aim of the present study was to evaluate the aternal risks in a series with an increasing rate of S and make comparisons of the complications tween emergency and elective C S associating em with the indications Studies were also made neonatal mortality and morbidity during these me conditions

FREQUENCY PARITY AGE

t Huddinge University Hospital 539 C S (6 4%) ere made among 8415 deliveries from October 1972 when the hospital was opened through June 1976 (Fig 1) As shown in Fig 1 there was a threefold increase in the frequency of C S during this almost four year period The number of children delivered by C S was 545 including four sets of twins and one set of triplets

In more than half of the patients (57 9%) Caesarean delivery was performed on primiparae Several patients were sectioned twice or thrice and two four times The patients with C S were 16–46 years of age with a predominance of 21–35 years (85 5%)

INDICATIONS

Indications for the 525 C S performed from 1973–June 1976 are summarized in Table I Only the main indication for each operation was recorded Patients with a pelvic outlet of less than 29 5 cm or between 29 5–31 5 cm (borderline) after X ray pelvimetry were summarized as cephalopelvic dis

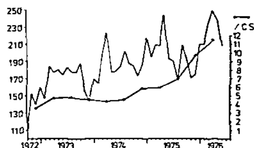


Fig 1 Number of deliveries every month from October 197?–June 1976 at Huddinge University Hospital C S ratio in % calculated three times per year

Table I *Indications for C S in % per year at Huddinge University Hospital 1973–June 1976*

	1973 %	1974 %	1975 %	1976 %
Vertex & cephalopelvic disproportion	37 9	27 0	17 5	25 4
Breech & cephalopel disprop or premat	15 5	12 2	17 5	18 0
Fetal distress	9 7	14 8	22 8	26 1
Placenta praevia	9 7	2 6	3 5	3 7
Abruptio placentae	1 9	4 3	5 8	3 7
Prolapsed unbilical cord	–	2 6	3 5	–
Diabetes mellitus	1 9	3 5	1 2	–
Toxaemia of pregnancy	4 9	7 0	3 5	4 5
Malpresentation	–	5 2	1 8	1 5
Uterine anomaly or uterine scar	1 0	2 6	1 2	0 7
Fetal growth retardation	–	–	1 8	1 5
Dysfunction of placenta	1 0	3 5	4 7	1 5
Serious maternal disease	2 9	–	1 8	2 2
Obstetrically old primipara	2 9	3 5	4 7	3 7
Psychiatric indication	2 9	0 9	1 8	2 2
Bad obstetrical history	1 0	2 6	2 3	0 7
Imminent uterine rupture	1 0	0 9	–	1 5
Previous corporal longitudinal incision	1 0	–	0 6	0 7
Uterine inertia	4 9	3 5	3 5	1 5
Miscellaneous	1 0	–	0 6	0 7

proportions (3) The same diagnosis incorporated a true conjugate of the pelvic inlet of less than 9 5 cm or a conjugate of 9 5–11 cm (borderline) Breech presentation delivered by C S was always combined with either cephalopelvic disproportion or prematurity Transverse lie mentum posterior and face posterior presentations are included under the heading of malpresentations Multiparity with a history of several intrauterine fetal deaths was registered as bad obstetrical history as were cases with previous complicated deliveries

OPERATIVE PROCEDURE

Induction of anaesthesia was made with a single dose of propanid (Epontol BAYER) followed by endotracheal intubation and maintenance of anaesthesia with nitrous oxide and oxygen [illegible] neurolept (Dridol LEO) Muscular relaxation was achieved by an intravenous dose of succinylcholine (Celocurin VITRUM) Epidural anaesthesia was given 10 times

A low midline incision was made in all women except in 67 (12 4%) where the Pfannenstiel method was employed The uterus was entered through a transverse lower segment incision Longitudinal incisions of the uterus were made in 10 cases because of previous cervico-corporal incisions transverse lie or placenta praevia

All patients were observed for 6–12 hours in the postoperative department and all children were taken care of by a paediatrician or by a trained anaesthetist

Additional surgery was performed in 19 cases (3 5%) Tubal sterilization was carried out in [illegible] women unilateral oophorectomies in two cases due to benign cysts ovarian resections in one woman for the same reason and oophorectomies [illegible] hysterectomy in one patient because of ovarian cancer Appendicitis was diagnosed in three women and a C S was made at the same time as the appendectomy

COMPARISON BETWEEN ELECTIVE AND EMERGENCY C S

Out of 539 Caesareans 241 were elective and 298 were made under *emergency* conditions The CS was made earlier than the 38th gestational week and

Table II *Complications during elective and emergency C S at Huddinge University Hospital Oct 1972–June 1976 Neonatal mortality Neonatal morbidity*

	Elective C S n=241=44 7% n of infants=241 (%)	Emergency C S n=298=55 3% n of infants=304 4 twins 1 triplet (%)
Complications		
(*a*) Intra operative	0 8	0 7
(*b*) Post-operative		
I Major complications	0 } 2 5	3 4 } 16 5
II Minor complications	2 5	13 1
Neonatal mortality	0 8	3 3
Neonatal morbidity	1 7	10 9

ıble III *Ten patients with major maternal com cations after delivery by Caesarean Section un r emergency condition at Huddinge University ɔspital October 1972–June 1976*

ɔamnionitis+peritonitis
amnionitis+peritonitis+ paralytic ileus Abscess of the Douglas pouch which was incised Wound infection
amnionitis Relaparotomy due to abscess in the uterine wall+ileus followed by sepsis The patient was nursed n an intensive care unit for 19 days
elaparotomy due to suspected intraabdominal haemorrhage
aralytic ileus Relaparotomy+secondary wound revi ion
sepsis
eritonitis+ileus Relaparotomy Stenosis of tracheae ost op Secondary sut of wound
traabdominal haemorrhage Relaparotomy followed sepsis and serious wound infection
ematoma+parametritis followed by septicaemia
of the patients with serious complications underwent laparotomies

r than the 42nd week in 92 of the patients 1%)

oth intra operative and post operative compli ions were encountered The post operative nplications have been divided into *major* and or ones

ntra-operative complications The number of a-operative complications was equal in both ctive and emergency C S Three bladder injuries re encountered and were duly sutured as was subcutaneous haemorrhage

Post operative complications Major post rative complications were only noted in *ergency* Caesareans (Table III) In five of the 10 ients with such complications re laparotomies I to be made *Minor* post operative adversities urred in 2 5% in the *elective* C S and in 13 1% the C S done under *emergency* conditions The st common complication was fever

There was one *maternal death* due to severe tox nia corresponding to a maternal mortality rate of per thousand of all abdominal deliveries and 0 1 thousand of all deliveries during this period of e The patient died five weeks after a C S from monary and cerebral abscesses and renal failure ere were ten neonatal deaths among the infants vered by *emergency* C S corresponding to a onatal mortality rate of 3 3% Seven of the in ts died of severe asphyxia and one of lethal con ital abnormalities Half of the 10 neonatal deaths were in the gestational age of 29–30 weeks and one in the 43rd week

Two of the infants delivered by *elective* surgery died during the neonatal period corresponding to a neonatal mortality of 0 8% The two mothers of the infants suffered from serious pre-eclampsia One weighing only 800 g was delivered in the 34th gestational week and died after a few hours from IRDS The other baby was delivered in the 39th week a boy weighing 1300 g and died from Potter s syndrome and a tentorium rupture

The registered disorders in the early neonatal period of the infants delivered by *emergency* C S was 10 9% compared with a rate of 1 7% in the *elective* C S group All children delivered by *elective* surgery and suffering from disorders in the neonatal period were at term In contrast 57 6% of the infants with neonatal morbidity in the *emergency* group were in the 31st–37th gestational week

The neonatal mortality rate for all C S was 2 2% and the total neonatal morbidity rate was 6 6% There was neither any morbidity nor any mortality of infants delivered by elective C S from healthy mothers at term

DISCUSSION

A threefold increase of C S (3 5–9 7%) has been observed at Huddinge University Hospital during the period October 1972–June 1976 This coincides with reports from several large obstetrical units in USA and Europe where a C S rate of 10–13% has been registered in the 1970s (4–6) A somewhat lesser rate however would be expected in the Scandinavian countries where a primary C S for example is not an indication for repeat Caesareans

A remarkably high frequency of C S in patients aged less than 20 and more than 35 has been noted by Plotho & Podesser in Austria in 1975 (8) This

Table IV *Fetal distress (asphyxia) as the main indication for C S October 1972–June 1976 in 103 patients (19 1% of all C S performed) at Huddinge University Hospital*

Asphyxia	1972 3 months	1973	1974	1975	1976 6 months
n	2	10	17	39	35

has not been our experience but might be due to many pregnant women in these age groups demanding abortion in Sweden

In the present study both the maternal and the neonatal morbidity rate of emergency C S exceeded that of elective section by 6 5 times Moreover the neonatal mortality rate was 4 1 times higher in the emergency than in the elective C S group Thus the elective C S can be regarded as a fairly safe procedure both for mother and child

Fetal asphyxia as an indication for C S has become more common during the period investigated (Table IV) In four years 103 cases of fetal distress were noted In 27 pregnancies (26 2% of all asphyxias) a combination of several prognostically severe indices were observed (low or falling estriol values intrauterine growth retardation as measured by ultrasound toxemia) In these high risk pregnancies spontaneous or induced labour by oxytocin resulted in CTG abnormalities which aroused clinical concern and the patients were delivered by *emergency* C S Babies born to such mothers (5% of all C S in our study) are known to exhibit glycogen depletion with higher neonatal mortality as well as morbidity (2 9 10) It is therefore our attitude to consider delivery by *elective* C S when the fetal hazards of vaginal delivery cannot be appraised This procedure might however still *increase* the C S rate

In the remaining asphyxia group the diagnosis of fetal hypoxia was based on CTG abnormalities which served as the sole indications for section It seems reasonable as shown by several authors (4 7) that a combination of CTG with fetal blood sampling could rule out several cases of suspected fetal depression and thus eventually *decrease* the rate of C S Such a prospective study is now in progress at Huddinge University Hospital

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Submitted for publication Feb 21 1977

Eva Patek
Dept of Obstetrics and Gynecology
Huddinge Hospital
S 141 86 Huddinge
Sweden

Acta Obstet Gynecol Scand 57 249–251 1978

AN INTRAVENOUS ^{133}Xe METHOD FOR MEASURING REGIONAL DISTRIBUTION OF PLACENTAL BLOOD FLOW

Jyrki Kuikka Kalevi Kaar Pentti Jouppila Tapani Pyorala and Ahti Rekonen

From the Department of Clinical Chemistry and the Department of Obstetrics and Gynecology University Central Hospital Oulu and from the Department of Obstetrics and Gynecology and the Department of Radiotherapy Central Finland Central Hospital Jyvaskyla Finland

stract A new method for measuring regional distribu n of placental blood flow is presented After 2–5 mCi of Xe saline has been injected intravenously the counts er the placenta are registered with a scintillation camera erfaced with a digital data storage and television read t system Using "area of interest technique time activ curves are obtained for different regions Analysis of curves is based on two-exponential curve fitting In rmal pregnancy the mean intervillous flow in 16 healthy men was 125 ml/min/100 ml and myometrial flow 17 /min/100 g The intervillous flow in the central part of placenta was 55% higher than in the marginal parts e myometrial flow in the placental area was nearly the ne as outside the placenta

scintillation camera interfaced with a digital com ter has been used for measuring the regional dis bution of blood flow in various organs e g brain lneys and myocardium As yet no way has been sented for evaluating the regional distribution of cental circulation though this would be of in est in clinical obstetrics especially in cases of ssible placental insufficiency

Recently Rekonen and co-workers (5) presented intravenous ^{133}Xe method for quantitative meas ment of placental blood flow The technique is n-invasive and uses single scintillation detectors ter i v injection of ^{133}Xe saline the tracer is tributed in the organism in the same proportion the blood in the systemic circulation With a gle detector one can only measure the circulation a particular organ area But by using a scintil ion camera with area of interest capabilities it possible to evaluate the regional distribution of w

This paper introduces a method for measuring the gional distribution of placental blood flow The thod uses intravenously injected ^{133}Xe saline as cer and the distribution of this is recorded with a scintillation camera interfaced with data storage and a fast television read-out system The intervil lous flow distribution in normal pregnancy is pre sented Simultaneously the regional myometrial flow is measured in the area of the placenta and outside this

MATERIAL AND METHODS

The test subjects were 16 healthy women with uncompli cated pregnancy mean age 26 years (range 18–37 years) The measurements were performed during the 35th–40th weeks of pregnancy

Before the measurements the patients refrained from smoking and rested on the measuring table for at least ten minutes The placenta was localized beforehand by an ultrasound B scan The patient lay in a 15 left lateral tilted position during the examination. The gamma camera head with low energy collimator (Radicamera) was aligned on the placental area A dose of 2–5 mCi of ^{133}Xe saline (gamma radiation energy 80 keV half life 5 3 d) was in jected rapidly into the cubital vein through a two-way syringe and flushed immediately with 10 ml of physiologi cal saline To diminish the escape of ^{133}Xe through the lungs the patient held her breath for 15–20 s after the injection To record quantitative data from the placenta a data storage (PDP 8 12 *k* words) and read-out system with fast television techniques (Nukab) was connected to the scintillation camera The data in digital form were gathered using 64×64 image matrices with a 10 s channel width over 10 min After the measurements the data were transferred to the magnetic disc The areas of interest were marked on the placental image for quantitative analysis The analysis areas were whole placenta three placental subregions and myometrial tissue outside the placenta (Fig 1) The total data density over the placenta ranged from 200 to 2 000 counts per cm The peak count rate was 1 000–10 000 counts/10 s

CALCULATIONS

The time activity curve of each area was fed in off line mode into a central computer (NOVA 840

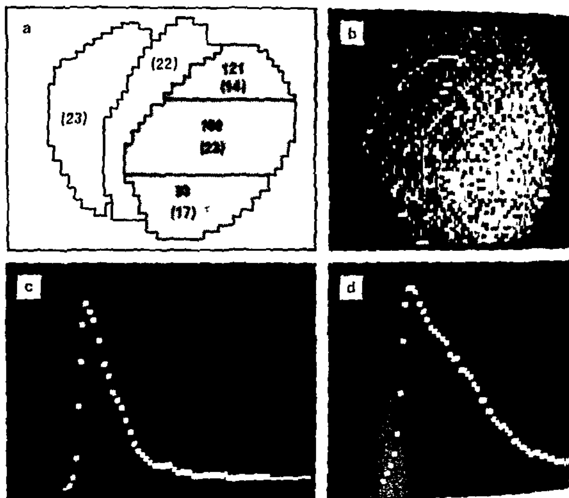


Fig 1 The regional distribution of blood flow in the placenta and myometrium The mean flow in the intervillous space is 141 ml/min/100 ml and in the myometrial area 19 ml/min/100 g (*a*) Distribution of flow the shaded area the placenta Figures without brackets refer to the intervillous flow and with brackets to the myometrial [illegible] (*b*) The original gamma picture of the placenta (*c*) Curve [illegible] registered over the whole placental area (*d*) Curve [illegible] istered over the myometrial area outside the placenta

64 *k* words) for processing A two-exponential function $(A_1 \exp(-k_1 t) + A_2 \exp(-k_2 t))$ was fitted to the measured washout curve using the least square method The fast component describes the fractional removal $(dQ(t)/dt = -k_1 Q(t))$ of the tracer from the intervillous blood pool The regional intervillous flow (in ml/min/100 ml) was calculated from the equation

$$F_1 = 100 k_1 \quad (1)$$

and the myometrial flow (in ml/min/100 g) from the slow component by using the conventional washout equation

$$F = p \cdot k \quad (2)$$

where *p* is the partition coefficient between [illegible] and myometrial muscle (=70 ml/100 g [illegible] 45%)

The radiation dose to the foetus with [illegible] activity of 5 mCi is less than 2 mrad

RESULTS

In the whole placental area the mean inter[illegible] flow was 125 ml/min/100 ml with a standard [illegible] tion of 45 ml/min/100 ml The myometrial [illegible] the placental area was 17±7 ml/min/100 g [illegible] side the placenta 16±7 ml/min/100 g The [illegible] between myometrial flow values in [illegible] the placental area is not statistically [illegible] ($p > 0.05$)

g 1 shows a typical regional distribution of the villous and myometrial flows In ten cases re the low ^{133}Xe dose (2 mCi) was used the nt rate in the small subregions was too low for ible regional analysis When the higher dose (5) was injected this analysis was possible (6 s) In all but two of these women the flow in the ral part of the placenta (155 ml/min/100 ml) was average 55% higher than in the marginal parts ml/min/100 ml) In the remaining two women whom the umbilical cord was situated in the ginal part of the placenta no clear difference found between the subregions of the placenta

DISCUSSION

e intervillous flow values presented here are the same magnitude as measured with other hods (2 3 4) Rekonen and co-workers (5) have lished results from 37 healthy women using the ^{133}Xe single detector method For intervillous they obtained a value of 135 ml/min/100 ml and myometrial flow 8 ml/min/100 g The intervil s flow is nearly the same as presented here but myometrial flow is clearly slower With the scin tion camera method the measuring area (area nterest) is delineated more exactly and the influ e of the low circulation in extramyometrial tis is smaller than in single detector measurements he myometrial flow in the placental area did not er significantly (4% higher) from the flow out This is in agreement with Rekonen et al (5) conflicts with the results of Jansson (4) who nd a significantly higher flow in the placental a

he picture of the regional distribution of the v shows that the circulation in the central part of enta is substantially higher (55%) than in mar al parts This is understandable because in these s the junction of the umbilical cord was ated in the area of maximal flow As the dis ution of blood flow is clearly non uniform le detector measurements may vary substantial This uncertainty can be avoided by choosing measurement area with the aid of gamma ures of the placenta (the area of maximal in sity)

hen the measurements of blood flow distribu n were made with the same activity (2 mCi) as single detector examinations the subregional lysis was not successful But although the activ ity has to be 5 mCi or more the radiation load is insignificant on both the mother and the foetus

The exact analysis presupposes that the tracer input into the intervillous space is an impulse bolus The i v injection actually leads to a broadening and recirculation of this bolus but these distortions are so slight that their influence on the results is in significant (under 10%) and exact deconvolution analysis is not necessary

The i v ^{133}Xe method for measuring the regional distribution of placental blood flow is atraumatic it is easy for the patient and the laboratory but does require a sophisticated scintillation camera computer apparatus The procedure takes 15–20 min of the patient s time and the analysis lasts about 20 min when the placenta is divided into subregions The method yields a large amount of quantitative information the situation and form of the placenta the intervillous flow and its spatial distribution and the myometrial flow The method is not suitable for studying a placenta situated in the posterior wall of the uterus In this paper the method has been used in normal pregnancy only Obviously it is also suit able for examining the distribution of placental blood flow in pathological situations

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Submitted for publication March 21 1977

Jyrki Kuikka
Department of Clinical Chemistry
University Central Hospital
SF 902?0 Oulu 22
Finland

Acta Obstet Gynecol Scand 57 253–255 1978

ULTRASTRUCTURE OF HUMAN UMBILICAL VEINS

Observations on veins from newborn children of smoking and nonsmoking mothers

Inger Asmussen

From the Department of Obstetrics and Gynecology YA Rigshospitalet University of Copenhagen Denmark

ract The umbilical vein was chosen as a possible lel for evaluating the vascular injury provoked by cco smoking in humans Umbilical veins from born children of 4 nonsmoking and 4 heavy smoking hers were examined in the transmission electron oscope Severe changes were present in the intima media of veins in the heavy smoker group Pro-ced edema was found in the subintimal space com d with destruction of intimal elastic membranes a sed decrease in collagen content and a proliferative tion of the myocytes Similar changes have been rved in animal studies involving exposure to carbon oxide hypoxia or nicotine The present study sup-s the concept that tobacco-smoking is harmful to the an vascular system and illustrates the mechanism ugh which the vascular injury is provoked in heavy kers The study also indicates that tobacco-smoking es severe damage during pregnancy to the cord Simi ronounced changes might be expected in the newborn lren of smoking mothers Tobacco-smoking should efore be abandoned during pregnancy Smoking dur regnancy carries a high risk for the fetus including an ased risk of abortion and stillbirth as well as death after delivery It is also well established that the age weight of newborn children of smoking mothers is 300 g less than that of those born to nonsmoking ers (1 5 11 12 17) The present study evaluates the structural changes found in the umbilical veins of born children of heavy smoking mothers compared a control group

PATIENTS

nant women admitted to the Department of Obstetrics Gynecology at Rigshospitalet were selected for the r All patients were examined by the same in gator and each patient completed a questionnaire on ting habits before and during pregnancy Eigh pa s took part in this study four smokers and four non ters The smokers had been heavily inhaling cigarette ters even before pregnancy The nonsmokers had r smoked

Women suffering from hypertension diabetes or other diseases and those with Rh negative blood types were excluded from the study The patients were somatically healthy before and during pregnancy and all laboratory investigations (hemoglobin blood glucose) including uri nary analyses for glucose and protein were normal Ran dom tests for urinary estriol during pregnancy revealed normal values

All the children were delivered at term were mature and no malformations were found The clinical data are presented in Table I In all eight cases the duration of labor was <12 hours

METHODS

Biopsy and preparation for microscopy

Immediately after delivery of the placenta a soft plastic catheter was placed in the umbilical vein and about 50 ml of cold Ringer s solution was infused from a syringe under light pressure

Perfusion was continued with 4 5% cold purified glutaraldehyde containing 2% acrolein and buffered to pH 7 4 with 0 2 M phosphate buffer for at least 5 min to prevent contraction during the cutting procedures

For the transmission electron microscopy the fixed vein was carefully dissected out cut into small blocks and immediately transferred to the same glutaraldehyde for 1 hour Postfixation was performed in 1% buffered osmium tetroxide (pH 7 4) for 1 hour at 4 C Tissue blocks were dehydrated in graded ethanols cleared in propylene ox ide and embedded in Araldite (Durcupan ACM) Sections 0 5–1 0 μm thick were stained with toluidine blue for light microscopy Ultrathin sections were cut on glass knives with an LKB Ultrotome III mounted on uncoated copper grids and contrasted with magnesium uranyl acetate and lead citrate These sections were examined and photo-graphed in a Zeiss EM 9S 2 electron microscope

The present study is an extension of earlier works on the umbilical artery (3) and the placenta (2)

The photographic work and the description of the morphology were completed and classified without knowledge of smoking habbits

Table I *Clinical data from eight children born to four non smoking and four heavy smoking mothers*

Cigarettes/ day	Weight	Sex	Placenta weight	± Days to term
0	3 900	M	600	+ 8
0	3 900	M	950	− 2
0	4 000	F	950	+ 6
0	3 800	M	750	+14
10	3 150	M	630	−21
15	3 350	F	900	+15
20	3 400	F	660	−10
20	3 343	M	750	− 6

RESULTS

Nonsmokers

The umbilical vein presented with an intima with an endothelial lining of continuous type with closed intercellular junctions a sparse media surrounded by adventitia The endothelial lining was resting on a non continuous basement membrane Just beneath the endothelial cells an internal elastic membrane or several elastic membranes were found In one of the nonsmokers mononuclear white cells were found on several sections of the tissue The endothelial cells were rich in fine filaments in the cytoplasm thus resembling the underlying myocytes with dense bodies All the usual organelles were present in the endothelial cells In the media and adventitia a characteristic finding was the huge amount of collagen fibers

Smokers

In view of the small number of patients only very striking observations have been recorded First of all edema was found It was located just beneath the endothelial cells and above the elastic membranes thus protruding the endothelial wall into the vein lumen But edema of the endothelial cells and the myocytes of media was also found The elastic membranes were split up by edema and invasion of myocytes There was a remarkable decrease in the collagen content of the media and adventitia By evaluating the collagen content and the presence of edema one could tell whether the tissue came from a smoker or a nonsmoker The basement membrane underlying the endothelial cells appeared normal

The endothelial lining also appeared normal although it was thinner than that of the [illegible] and lipid droplets were often found in the [illegible] somes Especially in the myocytes lots of [illegible] had accumulated

DISCUSSION

Tobacco smoking is a well-established [illegible] factor in the development of atherosclerosis [illegible] shown in population studies as well as in [illegible] exposure studies using hypoxia carbon [illegible] or nicotine (4 6 7 10 13 14 15 16)

Exposure to these agents causes severe [illegible] in the aorta and coronary arteries as well as [illegible] myocardium of experimental animals As a [illegible] model in which to demonstrate vascular and [illegible] damage provoked by tobacco-smoking in [illegible] the placenta and the umbilical artery and vein [illegible] chosen for this study

Severe damage was found in all the [illegible] from the heavy smokers compared with those [illegible] the controls (2 3) The morphological [illegible] could be classified as both degenerative and [illegible] tive

In the umbilical artery (3) as well as in the [illegible] ical vein edema was a characteristic finding [illegible] lar changes have been described in animal [illegible] studies Apparently leakage of the endothe[illegible] ing is a major component of the vessel damage [illegible] leading to subendothelial edema It is also [illegible] that other plasma components may pass the [illegible] thelial barrier and give rise to deposits of e g [illegible] or plasma lipids forming the developing [illegible] tous plaque

Also the well established proliferative [illegible] the media myocytes has been demonstrated [illegible] the umbilical artery (3) and vein In the [illegible] invasion of the broad basement membrane [illegible] found while in the veins the internal [illegible] membrane was split up The placenta from [illegible] smoking mothers showed similar changes [illegible] vessels but the most remarkable finding [illegible] obviously decreased vascularization ( )

During pregnancy three different products [illegible] formed the child the placenta and the [illegible] umbilical cord The above mentioned [illegible] demonstrated that tobacco-smoking during [illegible] nancy causes severe ultrastructural as well as [illegible] microscopical changes in the placenta and [illegible] cord Similar changes must be expected [illegible] children as well but the final proof is [illegible]

r ethical reasons Children born to smoking wom
i are small compared with controls (3 9) This
ight be due to damage to the child or sequelae to
sick placenta

In animal exposure studies pregnant animals
ewise gave birth to smaller offspring besides
oducing slightly fewer males (5 8) In humans
i it has been found that in a highly selected group
heavy smoking women about 80% of the
ildren were females whereas a control group
owed the normal distribution of male and female
ths in the population

At present these ultrastructural studies of the
ibilical vein artery (3) and placenta (2) are the
ly published data on the effects of tobacco
ioking during pregnancy in humans Further
idies are necessary but the present findings
ongly suggest that tobacco-smoking during preg
ncy is harmful In the author's opinion pregnant
imen should be advised to abandon tobacco-
oking

ACKNOWLEDGEMENTS

ish to thank Birte Kargaard for her generous and valu
e technical assistance

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Submitted for publication March 22 1977

Inger Asmussen
Dept Ultrastructural Research
Univ Instit Pathol Anat
University of Copenhagen
Frederik V's Vej 11
DK 2100 København Ø
Denmark

Acta Obstet Gynecol Scand 57 257–259 1978

CONJOINED TWINNING IN SWEDEN

Bengt Kallen and Goran Rybo

From the Department of Embryology University of Lund and the Department of Obstetrics and Gynecology Central Hospital Skovde Sweden

stract A small epidemic of conjoined twinning is orted occurring at the Skovde Central hospital in 75–76 Three pairs were observed the annual birth mber is 2300 During a ten year period 10 cases of njoined twinning were reported to the Register of Conntal Malformations in Sweden indicating a probable idence of 1 75000 births These 10 cases were distri ted all over the country Interviews with the three omen who gave birth to the Skovde conjoined twins re aled no common factor which could be of aetiological nificance

cently Bhettay et al (2) reported an apparent rease in conjoined twinning in southern Africa th 11 cases born during just over 12 months As essed by Hanson (3) the actual incidence cannot evaluated from the figures given and the served value could agree with the 1 50000 rate nerally thought to be the true rate of conjoined inning Earlier Milham (5) gave some evidence a clustering in time and space of cases of con ned twinning in the state of New York He col ted ?? cases from the 3 65 million births official registered during 1945–June 1965 a rate of 166000 This was probably an underestimate of true incidence Twelve of the sets of twins were m during 1955–1959 (6 expected) and 6 of these re born in 1959 Five of the latter were born thin a region of western New York within 50 les from each other The malformation surveil ice system in Atlanta (1) found an indication of istering during 1970–71 no cases of conjoined inning were found during 1968–69 three each in 70 and 1971 two in 1972 The possible presence small epidemics of conjoined twinning sug sts that exogenous causes may exist

Our interest was excited by the observation of ree cases of conjoined twinning during a little ore than one year in one hospital Skovde Central spital with approx 2300 annual births One case of thoracopagus was born in April 1975 and another in June 1976 During the same period a late legal abortion was performed on a young girl and the 21 weeks old fetus was dicephalic As births are only registered officially in Sweden after 28 weeks it was not notified as a case of conjoined twinning It would however have been included in a study similar to that of Milham where the age limit was 20 weeks

We report here on this small epidemic and the results of a survey of cases of conjoined twinning reported to the Swedish Register of Congenital Malformations

THE SKÖVDE CASES

The first birth of conjoined twinning in Skovde Central hospital occurred in April 1975—at 34 weeks gestational age The mother was a 34 years old house wife with three previous normal de liveries The twins were thoracopagus boys de livered by caesarean section and were stillborn

The second case was the legal abortion which was performed in September 1975—corresponding to a gestational age of 21 weeks The woman was an 18 years old school girl with no previous pregnan cy She was delivered after extraamniotic Rivanol installation of a dicephalic male fetus

The third case was born in June 1976 at a gesta tional age of 42 weeks approximately a month after the former case The twins were female thoracopagus They were delivered by caesarean section and were live born but an attempt at sep- aration failed and the infants succumbed The mother was a 30 years old house wife who had one earlier normal delivery

All three women were questioned about exposure to possible teratogenic agents and for family history of malformations or twinning The only twinning

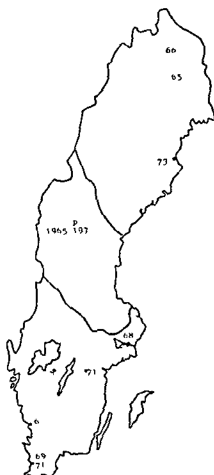


Fig 1 Map of Sweden with location of cases of conjoined twinning reported to the Register of Congenital Malformations and with the year of birth marked *S* marks location of the city of Skovde

found in the families was dizygotic twins on the husband s side in one of the cases No similarities were found with respect to factors such as drug use exposure to chemicals in the environment and radiation

THE REGISTER OF CONGENITAL MALFORMATIONS

Since 1965 there has been a compulsory reporting system in Sweden the Register of Congenital Malformations (4) Infants born after 28 weeks gestation are included A certain underreporting occurs to the register estimated to be about 20–25% for serious malformations When an infant is reported diagnoses are checked and verified The infants entered under the diagnosis conjoined twinning can be assumed to be correctly described and such infants cannot be entered under other diagnoses such as monsters

During the 10-years period 1965–1974 10 cases of conjoined twinning were reported The original patient records of these cases have been scrutinized The total number of births among hospitals reporting to the register during these years is approximately 878 500 which gives an incidence of about 1 88 000 Only symmetrical conjoined twins are included not cases of heteropagus As mentioned some underreporting may have occurred but it is probably low for such a spectacular malformation as conjoined twinning and an incidence of 1 75 000 in Sweden during this time period seems to be a reasonable estimate

The births of conjoined twins are fairly well scattered over Sweden (Fig 1)—the only hospital which had two such births during a ten year period was Malmo hospital (approx 3 500 annual births) The yearly distribution was also even 2 cases occurred each year in 1965 1966 and 1971 one case in 1968 1970 and 1973 none in 1967 1972 and 1974 The month of the last menstrual period was also evenly distributed 2 in January April and May none in March and June one in each of the remaining months Four pairs were boys six were girls Maternal age distribution was wide from 19 to 45 years The ten women had together 15 earlier pregnancies One ended as a legal abortion and three as miscarriages (2 in one woman) Among the 11 infants born one was a stillbirth

DISCUSSION

The normal rate of conjoined twinning is uncertain When routine vital registration is used for estimates an underestimate is probably obtained as cases may be reported without malformation diagnosis or as monsters The 1 166 000 rate reported by Milham from New York (5) is probably too low Ascertainment from hospital records is on the other hand with necessity based on only few cases For example the much quoted figure of 1 50 000 from Potter (6) represents only two cases It is also probable that a bias is obtained towards too high figures as the search of the records has often been made because of the birth of one or more cases of conjoined twinning at one hospital If the studies reviewed by Rudolph et al (7) are added an incidence of 1 31 000 is obtained which is probably too high The very varying figures which can be

btained with different methods of ascertainment e well illustrated by Hanson (1975)

We think that a figure of 1 75 000 as obtained om the central register can be a fairly adequate timate of the true incidence in Sweden This is lower than the figure usually quoted 0000 This may be explained partly by the sence of the bias just mentioned as data were llected as part of a routine registration of all alformed infants The exclusion of cases with a stational age below 28 weeks may also be a con tory factor and so is the inclusion of only asonably symmetrical twins Thus in Milham s aterial (5) 4 of the 22 pairs were delivered before eek 28 and in the Atlanta material one of the nine ses was a parasitic fetus (heteropagus)

If the incidence of 1 75 000 is accepted as a asonable estimate of conjoined twinning inci nce in Sweden the probability of two cases oc rring within nine months (calculated from LMP ates) in Skovde with 2 300 annual births is very w The improbability that this has occurred by hance is further strengthened by the phenomenon at within one month before the conception of the cond case another conjoined twin pair was con ived although aborted legally before reaching rm

If the three cases occurred as the result of an ogenous influence its nature has not been entified The women lived at different sites had fferent occupations neither used any drugs nor called infections

There are two possible ways in which an increase conjoined twinning can occur One is an increase monozygotic twinning with a constant risk for velopment of conjoined twins the other is a con ant rate of monozygotic twinning but an increased sk of conjoined twinning It has been stated that increased incidence of twinning is found in milies where a case of conjoined twins is born g Rudolph et al (7) found a positive history of inning in 13 and a negative one in 6 of 65 re iewed families with conjoined twins) A doubling the rate of monozygotic twinning would appear s an approximately 30% increase in total twinning te The twinning rate in Skovde Central hospital in 1975 and 1976 was not significanty increased (40 cases found 37 expected)

The data presented in this paper deviate at one point from those usually described for conjoined twinning namely with respect to sex ratio It is generally stated that there is a marked predomi nance of female pairs For instance of Milham s 22 pairs (5) 20 were female one was male and one was a mixed male–female pair Rudolph et al (7) re viewed 60 cases with known sex—43 were female and 17 male However in the relatively recent Atlanta series of 9 cases (1) only 5 were female and in our series of a total of 13 cases 7 are female These two series thus give a near 1 1 sex ratio Is it possible that embryonic loss of male embryos could explain the high female dominance in earlier series? Perhaps better prenatal care reduces embryonic loss and that this results in a more even sex ratio in more recent series—and contributes to an increase of the total rate

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Submitted for publication Ap il 4 1977

Bengt Kallén
Department of Embryology
University of Lund
Lund
Sweden

Acta Obstet Gynecol Scand 57 261–264 1978

ON RECEPTORS FOR ESTROGENS (E_2) AND ANDROGENS (DHT) IN HUMAN ENDOMETRIAL CARCINOMA AND OVARIAN TUMOURS

L G Friberg S Kullander J P Persijn and C B Korsten

From the Gynecological Section Department of Oncology University Hospital Lund Department of Gynaecology Malmo General Hospital University of Lund Sweden and the Department of Clinical Chemistry Antoni van Leeuwenhoek Ziekenhuis Amsterdam the Netherlands

bstract Some human endometrial carcinomas contain ceptors for estrogen (E_2) and dihydrotestosteron (DHT) nalysis of 50 primary endometrial carcinomas by agar gel ectrophoresis revealed a varying receptor pattern sence of both receptors sole presence of E_2 or DHT ceptor or presence of both Highly differentiated mours often had receptors of both types (7/18) and orly differentiated tumours most often lacked them /10) Primary tumours with metastases (Stages III–IV) ldom had combined receptors only in 2 cases out of 9 rowth of the tumour down in the cervical canal (Stage II) nplied absence of combined receptors in all of the 13 ses studied In 8 different ovarian tumours presence of ther E or DHT receptors was found in 6 The findings e discussed in relation to hormonal treatment of the sease

is now generally accepted that endocrine therapy n induce regression of certain malignant tumours he effect of progesterone in the treatment of rcinoma of the uterine corpus has attracted much tention Particularly well differentiated lenocarcinomas seem to respond favourably while ss and un-differentiated neoplasms seem to be ther clinically resistant The best effects have en observed on pulmonary metastases in patients er 60 years (8) but also in local recurrences re ession in more than half of a series of 37 patients as obtained using only gestagen treatment (1) It ems possible that oestrogens also play a role for e responders (18)—maybe by stimulating target lls to synthetize receptor proteins for binding the ogesterone

In mammary carcinomas it has been shown that docrine therapy is of little value in the treatment f patients without demonstrable estrogen receptors the tumour tissue (2 3 7 9 14 and others) strogen receptors have also been found in the endometrium of postmenopausal women In 8 patients with endometrial carcinomas 6 were found to bind oestradiol specifically Specific binding of progesterone in the uterus also seems to exist (14 17) but whether endometrial carcinoma is hormone-dependent only in those cases where evidence of specific progesterone binding occurs in the malignant tissue is unknown Hitherto only small numbers of patients with endometrial carcinoma have been evaluated and mostly only for a single receptor oestradiol Knowledge of the receptor pattern for several steroids in a greater number of endometrial carcinomas might give an improved picture which would help to refine hormonal therapy This paper is concerned with the occurrence of oestradiol and dihydrotestosterone receptors in a large group of endometrial carcinomas the receptors being related to various parameters of the disease A study in breast cancer has shown evidence that determination of androgen receptors besides the oestrogen receptors would increase the likelihood of predicting clinical responsiveness to castration (3 15)

Some different ovarian tumours were investigated in this study in the same way as the endometrical carcinomas So far as is known no receptor determinations on human ovarian tumours have been published earlier

MATERIAL AND METHODS

Tumour material was obtained from patients who had not received previous irradiation or hormones Fifty patients with adenocarcinoma of the endometrium and eight with ovarian tumours were studied The diagnosis was based on histopathological criteria The stage of the endometrial cancers was classified according to the International Classification established in 1961 The tissue was collected by

Table I *Endometrial cancers*

No (n=50)	Patient age	Clinical Stage	Tumour grade of differentiation	
10	≤60 years	I	High	6
			Medium	2
			Low	2
6		II	High	2
			Medium	4
			Low	0
4		III–IV	High	1
			Medium	3
			Low	0
18	>60 years	I	High	7
			Medium	9
			Low	2
7		II	High	2
			Medium	2
			Low	3
5		III–IV	High	0
			Medium	2
			Low	3

curettage or at laparotomy Small pieces of the tumour was transferred to glass tubes deep frozen and stored until the receptor analysis A piece of the same tissue was retained for histological evaluation

Extracts of the tumour tissues were prepared as recommended at the EORTC workshop of September 19 1972 using a microdismembrator (Braun Melsungen Germany) Estrogen and androgen receptor were determined in the extract according to Wagner (21) using agar gel electrophoresis Incubation with the labelled hormone was done for about 16 hours The binding of estrogen ([6 7 ^{3}H]estradiol 17β 40 Ci/mmole) and androgen (5α dihydro[1,2 ^{3}H]testosterone 48 Ci/mmole) expressed as cpm per g tissue protein (counting efficiency 45%) Total protein was assayed using the biuret action Human serum albumin was assayed immunologically by single diffusion using Partigen plates manufactured by Behring Werke (Germany)

In a previous paper a statistical evaluation was given of the oestrogen binding capacities of benign and malignant human mammary tumours by probit analysis (9) For the discrimination of androgen receptors in breast tumours the same procedure was followed Intermediate estrogen receptor or androgen receptor values were regarded as positive The above cut off levels were also applied in the study of oestrogen and androgen binding capacities of endometrial and ovarian tumours

Clinical details of the endometrial cancer patients and the histopathology of their tumours are shown in Table I

RESULTS

The results of the receptor determinations in endometrial cancers are shown in Table II and on ovarian tumours in Table III

Table II *Receptors in endometrial carcin*

Pat	Stage	No receptors	E_r-DHT receptors	Solely E_r
Highly differentiated				
≤60 years	I	1	5	0
	II	1	0	1
	III–IV	1	0	0
>60 years	I	2	[illegible]	[illegible]
	II	0	0	[illegible]
	III–IV	0	0	0
Total		5	7	[illegible]
Medium differentiated				
≤60 years	I	1	0	1
	II	1	0	3
	III–IV	2	0	1
>60 years	I	5	1	1
	II	1	0	1
	III–IV	1	1	0
Total		11	[illegible]	7
Non differentiated				
≤60 years	I	1	0	1
	II	0	0	0
	III–IV	0	0	0
>60 years	I	[illegible]	0	0
	II	2	0	0
	III–IV[a]	2	1	0
Total		7	1	1

[a] One of these patients G H had skeletal meta the time of the receptor analysis Progesterone tr (500 mg Proluton Depot® 3 times weekly) was started In spite of this the metastases progress pulmonary metastases developed and the patie ter 3 months

[b] One of these patients S A had pulmonary me at curettage Progesterone treatment (500 mg Depot® 3 times a week) was started immediat therapy was without any effect and the patient d 2 months later

DISCUSSION

Our receptor findings confirm that there is re believe that certain ovarian carcinomas r spond to endocrine therapy Gestagen tr has been observed to be beneficial in cas pulmonary metastases from endometrial carcinoma (10) and there is clinical eviden progestagens may be more or less effective 10% of ovarian cancers Receptor measurem a large number of different ovarian tumors w of importance if followed by prospective m tions to find out whether the presence of re

ble III *Receptors of ovarian tumours*

ent	Type of tumour	E_2 receptors	DHT receptors
	Mucinous cystadenoma I A	−	+
	Mucinous cystadenoma II B	−	+
	Cystadenofibroma I B	+	−
	Cystadenofibroma I B	−	−
	Cystadenocarcinoma II C	−	−
	Mucinous cystocarcinoma II C	−	+
	Papillary ovarian cancer	−	+
	Papillary ovarian cancer	+	−

ovarian cancers really has a value in predicting ponse to endocrine treatment

Bonte (1) found that the metabolic and hormonal tus of the patient with endometrial carcinoma is st significant for the response of the tumour to gesterone therapy The good responders had ong other things an oestrogenic vaginal smear d complete regression was only obtained in stmenopausal patients whose initial estrogenic ginal smear showed atrophy following gestagen atment Obviously those ideal patients had en genous oestrogens and both oestrogen and pro sterone receptors in their vaginal mucosa—and en probably also in their endometrium Influences om sex hormones in postmenopausal women have en found to run parallel in vagina and uterus by any authors using different substances (11)

In our material growth of the endometrial cancer wn the cervix canal (Stage II) usually meant sence of combined receptors or DHT receptors HT is an oestrogen antagonist (anti-estrogen) d may like progestagens be useful in the treat nt of neoplastic changes of the endometrium

In our material tumours with metastases (> age II) had relatively seldom combined hormonal ceptors This may explain the failures of en crine treatment

Since the presence of sex steroid receptors in a sue is indicative of its being a target tissue re ptor measurements may offer a means for select g patients with endometrial carcinoma stages III d IV for endocrine therapy

Two cases mentioned in detail in Table II and lacking receptors were both treated with progesterone but soon died No other cases of ours were treated with progestagens

No information is found in the literature on the receptor content of primary endometrial cancers and various secondary tumour deposits analysed at the same time In different metastases in the same patient there might be different receptor situations due to different cell clones as has been shown for human ovarian tumours in work with other cytostatic agents (12) If no receptors are found in the primary lesion there is little prospect that receptor function is regained in metastatic cell deposits or that hormonal treatment will be successful On the other hand if receptors are found in the uterine tumour tissue this does not necessarily mean that all or any metastases possess the same receptors

When demonstrating the occurrence of oestrogen hormone receptors an error might lie in the possibility that in these cases abnormal receptors may occur The receptor molecules of the tumour cells bind the hormone but may fail to translocate to the nucleus (13) Such false positive cases with abnormal receptors could not be expected to respond

Radiotherapy may destroy some receptor proteins and thereby also lessen the chances for a hormonal response or influence on the local tumour

The estrogen receptor concentration of human normal endometrium has been stated (5) to be highest in the early proliferative phase of the menstrual cycle and in the postmenopausal state to be similar to that seen in the proliferative endometrium In 8 studied cases of endometrial carcinoma according to Evans et al (5) there seemed to be a correlation between the stage of differentiation of the tumour and the receptor concentration being highest in the well differentiated tumours This was in agreement with results in 9 cases attained by Terenius et al (20) but contradicted findings of Taylor et al (19) Our findings showed that highly differentiated tumours certainly have more often E_2 receptors (12 cases out of 18) than non-differentiated (2 out of 10) They also more often possess receptors of both E_2 and DHT types

In 15 cases of endometrial carcinoma studied by Pollow et al (16) the highest concentrations of E^2 receptors were found in undifferentiated carcinoma which on the other hand showed the lowest concentration of progesterone binding Negative findings

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Highly differentiated						
≤60	I	1	5	0	0	
years	II	1	0	1	0	
	III–IV	1	0	0	0	[illegible]
>60	I	2	[illegible]	[illegible]	1	
years	II	0	0	[illegible]	0	
	III–IV	0	0	0	0	[illegible]
Total		5	7	5	1	[illegible]
Medium differentiated						
≤60	I	1	0	1	0	
years	II	1	0	3	0	
	III–IV	2	0	1	0	[illegible]
>60	I	5	1	1	[illegible]	
years	II	1	0	1	0	
	III–IV	1	1	0	0	[illegible]
Total		11	2	7	[illegible]	[illegible]
Non differentiated						
≤60	I	1	0	1	0	
years	II	0	0	0	0	
	III–IV	0	0	0	0	
>60	I	2	0	0	0	
years	II	2	0	0	1	
	III–IV[b]	2	1	0	0	[illegible]
Total		7	1	1	1	[illegible]

One of these patients G H had skeletal metastases [illegible] the time of the receptor analysis Progesterone treatm[illegible] (500 mg Proluton Depot® 3 times weekly) was then [illegible] started In spite of this the metastases progressed an[illegible] pulmonary metastases developed and the patient died [illegible] ter 3 months

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DISCUSSION

Our receptor findings confirm that there is reas[illegible] believe that certain ovarian carcinomas ma[illegible] spond to endocrine therapy Gestagen trea[illegible] has been observed to be beneficial in cases [illegible] pulmonary metastases from endometrial car[illegible] carcinoma (10) and there is clinical evidence th[illegible] progestagens may be more or less effective in ab[illegible] 10% of ovarian cancers Receptor measurements [illegible] a large number of different ovarian tumours w[illegible] of importance if followed by prospective stu[illegible] tions to find out whether the presen e of re[illegible]

Acta Obstet Gynecol Scand 57 265–271 1978

PREGNANCY AND SARCOMA

Kianoosh Jafari Abraham F Lash and Augusta Webster

From the Department of Obstetrics and Gynecology of the Cook County Hospital and the Department of Obstetrics and Gynecology of the University of Health Sciences/The Chicago Medical School Chicago Illinois

stract Six cases of pregnancy associated with sarcoma presented Among these six cases is one patient with var sarcoma which was diagnosed during the 34th week regnancy The literature was reviewed with reference he effect which pregnancy may have on the growth of lignant tumors Most authors believe that pregnancy no deleterious effect on the course of cancer how r this is not well supported through adequate data eral reports to the contrary contain evidence that preg cy may have a deleterious effect on the course of cer These discrepancies could be explained on the s of differences in the natural history and biological avior of different malignant tumors in relation to the gnancy

association of pregnancy with sarcoma is rela ly rare The management of a patient with this dition includes the question as to whether or not gnancy may have adverse effects on the growth of the tumor The treatment depends on the of lesion anatomic location stage of the dis e and age of the gestation (1 2)

he recent management of a patient with astatic liposarcoma prompted us to review our or files which contain 5 other cases of preg cy complicated by sarcoma Table 1 shows a ical summary of our patients with sarcoma and gnancy who were treated at Cook County spital

n this paper we are presenting a review of the ature and our 6 cases

CASE REPORTS

1 (C H)

 35-year-old white female gravida ? para 1 was itted with complaint of labor pains She was pregnant m and had dyspnea orthopnea and marked edema of wer extremities Fetal heart tones were normal The x was thick and closed A chest X ray revealed iple round densities in the right lung field suggestive ulmonary metastases Because of heart failure the patient was placed on nasal oxygen and digoxin A week after admission her general condition deteriorated progressively and under local anesthesia a classical Cesarean section was performed A live term female infant was delivered Evisceration occurred on the eighth postoperative day and was repaired Subsequently she became febrile and expired on the eleventh postpartum day (4) Postmortem examination revealed a 10×8×6 cm mass located in the posterior and medial aspect of the right leg Histological examination revealed pleomorphic sarcoma There were multiple metastases to both lungs

Case 2 (R H)

This 3? year-old female gravida 11 para 10 was admitted to Cook County Hospital in March 1953 with a history of abdominal pain of two days duration She was 7 months pregnant and had been bedridden for four months following a fall at home

Physical examination revealed an emaciated female with a limp right arm and atrophy of the right leg Fetal heart tones were normal Bone X rays revealed generalized osteoporoses and sclerosis of the skull Blood chemistry revealed elevation of serum calcium and alkaline phosphatase Eight days after admission she went into labor and delivered a 2210-gram infant in good condition X rays of the infant revealed normal bone structures

A bone marrow biopsy of the patient revealed metastatic tumor cells The patient expired on the 89th postpartum day (5) Autopsy revealed a benign parathyroid adenoma and an osteogenic sarcoma.

Case 3 (S P)

This 36-year-old white female gravida 4 para 2 abortus 1 was admitted to the hospital on August 5 1960 because of jaundice chills and fever of one week s duration She had a history of lymphosarcoma which was treated with X ray in 1955 A diagnosis of pulmonary tuberculosis had been made in 1957 She did well until 1958 when the lymphosarcoma became symptomatic again for which she received another course of X ray therapy

Physical examination on admission revealed a severely icteric debilitated female She had a blood pressure of 1?0/80 mmHg pulse rate of 140 per minute There was a systolic murmur at the apex of the heart rales and ronchi at the base of the left lung She had hepatosplenomegaly and the uterus was enlarged to 3? weeks gestational size Fetal heart tones were normal





Figs 1 and 2 Gross and microscopic examination of vulvar tumor in case 4 (Z J) showing malignant mixed mesodermal tumor compatible with sarcoma botryoides

The patient was treated with intravenous fluids antibiotics steroids and anti tuberculosis drugs After some improvement she went into labor on the 4th hospital day and delivered a 1390-gram live infant Despite intensive medical treatment the general condition of the patient deteriorated and she expired on the 11th postpartum day

Case 4 (Z J)

This 39 year-old female gravida 15 para 4 was admitted at 34 weeks gestation to Cook County Hospital with a complaint of a painful mass in the vulvar region She first noted this as a small mass ten months prior to her admission It subsequently increased in size during the pregnancy and became symptomatic a few days prior to admission She was known to have diabetes mellitus since 1958 and was controlled on 45 units of NPH insulin daily during pregnancy

Physical examination revealed a 264 pound female who was not in acute distress She had a blood pressure of 140/90 mmHg a pulse rate of 120 per minute and a normal temperature Heart sounds were normal and the lungs were clear Her uterus was enlarged to a 36 weeks gestational size The fetal heart tones were normal There was a fist size mass arising from the left side of the vulva obstructing the introitus Rectal examination revealed a floating head and closed cervix Her blood glucose ranged from 86 to 174 mg per 100 ml and the chest X ray was normal the VDRL test was negative and the hemogram showed hemoglobin of 10 8 g

Suspecting a Bartholin gland abscess incision and drainage were attempted but no fluid was obtained A biopsy was performed and reported as myosarcoma

One week after admission the patient went into [illegible] A Cesarean section was performed and a female [illegible] delivered The post partum course was uneventful

The patient was given 3 700 rads external radiation [illegible] the perineum which decreased the size of the tumor [illegible] kedly this was followed by local wide excision of the tumor 2 months post partum Pathological examination [illegible] the specimen revealed a mass measuring 7 0×6.5× [illegible] and weighing 98 g The bulk of the tumor consisted [illegible] firm pale yellow tissue Microscopic examination of [illegible] tumor revealed a mixed mesodermal tumor compatible with sarcoma botryoides (Figs 1 and 2) The patient [illegible] lost to follow up since 1963

Case 5 (M C)

This 22 year-old Negro female gravida [illegible] para 1 [illegible] admitted to Cook County Hospital in August 19[illegible] [illegible] was 38 weeks pregnant and gave a history of a previous Cesarean section She had a giant cell tumor of the [illegible] treated in 1969 by wide excision of the tumor

Physical examination revealed a 38 weeks gestation size uterus and normal fetal heart tones There was [illegible] surgical scar on the lower aspect of the left leg One [illegible] after admission the patient underwent a Cesarean section and tubal ligation A 2450-gram live male infant [illegible] born She was discharged on the eighth postoperative [illegible] At present the patient is living with no evidence of [illegible] ease

Case 6 (T N)

A 15 year-old black female was admitted to Cook County Hospital on September 21 1975 in the third [illegible]



3 Chest X ray of case 6 (T N) showing opacification
ie left hemithorax due to metastitic liposarcoma

nancy complaining of right sided chest pain of four duration and productive cough with yellow sputum ree weeks duration She had a history of anaplastic arcoma of the right thigh treated by 2 000 rads exter adiation followed by a 5-day course of Actinomycin D e microgram per kg per day) and partial resection of ior thigh muscles on the third day of chemotherapy in st 1973 She did well and remained asymptomatic November 1974 She was then lost to follow up this admission she had shortness of breath requiring en therapy by mask Her heart sounds were normal ulse rate was 100 per minute and her blood pressure 130/80 mmHg She had decreased breath sounds over ight hemithorax and dullness on percussion of the t posterior lung field Her uterus was enlarged to a 32 gestation Fetal heart tones were normal The ix was soft and admitted one finger tip There was an urgical scar on the right thigh The hemoglobin was white blood cell count was 10 000 her liver le and blood chemistry were normal the coagulation le was normal urinalysis and urine culture were un rkable

r chest X ray showed opacification of the entire right thorax (Fig 3) The trachea was slightly shifted to the side The findings were consistent with collapse of ight lung thought to be due to occlusion to the right stem bronchus Superior vena cavagram revealed a in the right side of superior mediastinum causing nsic compression of the distal portion of the superior cava and both innominate veins Esophagogram showed narrowing of the middle portion of the esophagus suggestive of extrinsic pressure Ultrasound examination of the abdomen revealed a fetal biparietal diameter consis tent with a 31–32 week gestation Cytology of bronchial washing was reported as Class II A bronchoscopic biopsy specimen was reported as poorly differentiated lipo-sarcoma metastasizing to bronchial tissue

On October 6 1976 the patient was started on external radiation to the mediastinum with shielding of the abdo-men Ten days later she went into labor which lasted for four hours and delivered a 1 815-gram male infant with an Apgar score of 10 The postpartum course was uneventful and radiation treatment was completed on October 30 1975 with a total dose of 3 900 rads to the mediastinum This was followed by a 7-day course of multiple drug chemotherapy consisting of Adriamycin 20 mg intrave nously three doses Cytoxam 400 mg intravenously two doses and 5-(3 3-dimethyl-1 triazeno) imidazole-4 carboxamide (DTIC) 300 mg intravenously two doses The patient was heparinized with 5 000 units every 4–6 hours during the course of chemotherapy After the first course of chemotherapy the general condition improved markedly she no longer required oxygen her voice im-proved and the dysphagia subsided Because of severe bone marrow supression the second course of chemo-therapy was started four weeks later with reduced doses and continued with 2–3 week intervals due to the patient s condition Sequential X rays (Figs 4 and 5) showed im-provement of the involved lung At present the patient is in remission and her general condition is good

DISCUSSION

xistence of genital sarcoma and pregnancy is an remely rare condition A case of endometrial oma causing obstructed labor was reported by (6) in which the infant was delivered by arean section In 1972 Kececioglu (7) reported ise of sarcoma botryoides of the cervix coinci t with first trimester of pregnancy The patient treated by total abdominal hysterectomy and teral salpingo-oophorectomy followed by 6000 s external irradiation Sarcoma botryoides aris from the vagina coincident with pregnancy has been reported (8)

arcoma of the vulva is a very uncommon lesion t investigators noted that this lesion is more ly to occur in patients between the ages of 30 to but it has been reported in a 4-month old infant well as in a newborn (9) From the late 19th ury to the present as nearly as we are able to rtain only 4 cases of sarcoma of the vulva ciated with pregnancy including our case have n reported (9) In 1957 Nolan (10) reported a of sarcoma arising from the base of the hy al ring in a 23 year old pregnant patient In Lygyi (1) and co workers reported two cases regnancy complicated by Ewing s sarcoma of pubic bone in one and reticulum cell sarcoma of erineum in the other They noted a remarkable leration of tumor growth during pregnancy and l metastatic spread during the postpartum od Priore and co-workers (9) in 1966 reported a of fibrosarcoma arising from the right labium is in the fifth month of pregnancy The patient treated by hemivulvectomy without node dis on

is of importance to the clinician to know ther or not pregnancy has any adverse effect on rowth of the malignant tumor

e analysis of a available data does not suggest pregnancy has any deleterious effect on the se of sarcoma Treves & Holleb (11) compared groups of pregnant and non pregnant women breast cancer and found a higher incidence of ive axillary nodes in a group of pregnant patients White and co-workers (12) reported a 73 3% five year survival in a group of 30 patients with melanoma and pregnancy versus 54% five year survival in a group of 31 non pregnant women They concluded therefore that pregnancy does not have adverse effects on survival of patients with melanoma George and co-workers (13) reviewed 115 cases of melanoma associated with pregnancy and 330 controls from Memorial Hospital They demonstrated that there is a higher incidence of regional node metastasis in pregnancy but the clinical course of melanoma in both groups was the same

Shev and co-workers (14) recently reported a series of 251 patients with melanoma associated with pregnancy One hundred and sixty five had Stage I disease and 86 patients had Stage II (regional node metastases) In Stage I the overall survival rate was 84% with no significant difference between the two groups however in Stage II the survival rate was significantly lower in pregnant patients than in nulliparous patients 29% and 55% respectively

Cantin and co workers (15) reported a series of 205 premenopausal women 57 of whom became pregnant during the course of management of sarcoma These 57 patients had a total of 83 pregnancies which occurred either simultaneous or subsequent to the treatment of sarcoma or after the appearance of the tumor but before initiation of therapy They compared the 89% five year survival rate in a group of nine patients with liposarcoma associated with 13 pregnancies with a 66% five year survival in a group of 29 non pregnant patients of childbearing age They concluded that there was no adverse effect of pregnancy on the survival rate of women with liposarcoma They mentioned similar observations among other types of soft tissue sarcomas Of great interest is one of their patients who had a slow growing tumor on the thigh noted at age 34 At age 39 she became pregnant and the tumor grew larger therefore it was excised and pathological examination of the tissue revealed liposarcoma At age 47 she became pregnant again The tumor recurred on the thigh and another primary sarcoma appeared on her neck Most authors believe that pregnancy does not increase the potentiation of growth and metastatic spread of sarcomas This evaluation has been made by comparing stages of cancer and survival rates in pregnant and non pregnant patients Therefore as with

Chest X ray of case 6 (T N) after irradiation for static liposarcoma showing improvement in the in d lung

Chest X ray of case 6 (T N) after irradiation and otherpy for metastatic liposarcoma showing im ment in the involved lung

Table 1 Summary of cases of sarcoma and pregnancy treated at Cook County Hospital

Case	Year of delivery	Age	Gravida	Para	Type and location of sarcoma	Treatment	Fetal outcome	Survival at time of report
1 (C H)	1948	35	2	1	Sarcoma (unspecified) of the right leg with pulmonary metastasis	Digoxin Oxygen Cesarean section	Live female	Expired on [illegible] postpartum [illegible] Autopsy [illegible]
2 (R H)	1953	32	11	10	Osteogenic sarcoma	Spontaneous delivery	Live infant 2210 g	Expired [illegible] after delivery Autopsy [illegible]
3 (S P)	1960	36	4	2	Lymphosarcoma	Spontaneous delivery	Live infant 1 390 g	Expired [illegible] after delivery
4 (Z J)	1961	39	15	4	Malignant mixed mesodermal tumor of vulva compatible with sarcoma botryoides	Cesarean section External irradiation (3 700 rads) followed by wide local excision of the tumor	Live female infant	Lost to follow up after 3 months
5 (M C)	1972	22	2	1	Giant cell tumor left leg treated in 1969	Cesarean section and tubal ligation	? 450 g live male infant	No evidence of disease
6 (T N)	1975	15	1	0	Liposarcoma of thigh treated in 1973 *Metastasis to the* lungs appeared during pregnancy	External radiation to mediastinum Vaginal delivery Chemotherapy	1 815 g live male infant	In remission

any other retrospective studies it is difficult to find a control group which could properly match the study group One may argue that a patient with sarcoma who becomes pregnant is very likely in better physical condition than the one who does not become pregnant

Sholket and Fortner studied transplantation of melanoma in pregnant and non pregnant hamsters and found that pregnancy did not stimulate either the development or the metastatic spread of the disease (13)

The report of Shiv and his colleagues revealed a lower survival rate in Stage II melanoma associated with pregnancy compared with non pregnant women Nevertheless individual case reports from other series reveal progression or re*currence of the disease during pregnancy suggesting* the possibility of a deleterious effect of pregnancy on the course of sarcoma

As is shown in Table I in our series all pregnancies terminated to the delivery of viable infants Therefore when the disease is localized appropriate treatment should be instituted but when the disease is widely spread and there is not much hope for survival the fetus should be given *the primary* consideration Fetal or pla[illegible] metastatis is a rare condition Of the [illegible] maternal cancer metastasizing to the placenta [illegible] fetus 14 have been malignant melanoma [illegible] of chorionic villi is associated with poor fetal [illegible]come (3)

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Submitted for publication July 25 1977

K Jafari
Department of Obstetrics and Gynecology
Cook County Hospital
1825 West Harrison Street
Chicago Illinois 60612
USA

Acta Obstet Gynecol Scand 57 273-276 1978

CERVICAL ADENO CARCINOMA AND PARTIAL HYDATIDIFORM MOLE

Benjamin Mazor Amicam Bar Am and Liane Deligdish

Institute of Pathology Ichilov Hospital and Department of Obstetrics and Gynecology A Maternity Hospital Hakiryah Municipal-Governmental Medical Center Sackler School of Medicine Tel Aviv University Tel Aviv Israel

bstract Partial hydatidiform mole was found in a 39-ar-old grand multiparous Jewish woman having a lypoid cervical adeno-carcinoma The patient was eated by surgery followed by internal and external pelvic adiation with excellent results Four and a half years ter the initial diagnosis she is very well This is the first ported case of a rare combination The literature regard g the association between pregnancy and cervical alignancies is reviewed briefly and the possible patho-netic relationship between hydatidiform mole and rcinoma of the cervix is discussed

o the best of our knowledge the simultaneous curence of hydatidiform mole and cervical lenocarcinoma has not been reported in the edical literature before

Krimmenau & Ganghanel (8) in 1960 reported case of invasive mole occurring in a 45 year-old oman with squamous cell carcinoma of the cervix at tumor was macroscopically small and had read to the inguinal lymph nodes

CASE HISTORY

39 year-old woman was first seen in our out patient nic in April 197? She was complaining of low abdomi l pain back ache and a whitish gelatinous vaginal dis arge for a few weeks She had seven normal preg ncies and deliveries in the past and one twin delivery r periods were every 23 to 30 days The last one had en on 4th March 197? On physical examination her neral condition was good No palpalable abdominal or hic masses were found Vaginal examination revealed uterus slightly enlarged with both parametria and the uch of Douglas free A soft solid grey coloured mass asuring approximately 3×2×4 cm was protruding from external cervical os through a pedicle The mass did t bleed on touch A white gelatinous vaginal discharge s also noticed

All routine blood and urine tests were normal Chest ray was negative Excision of the cervical tumor was rformed under general anesthesia without any particu difficulties Histologically it was found to be a polypoid ll differentiated adenocarcinoma of the cervix uteri uch consisted of irregularly crowded mucus secreting glands The connective tissue between them was scanty The epithelial cells although most of them well differentiated and mucin producing showed irregularities nuclear and cellular atypias as well as numerous atypical mitoses However the general pattern was glandular with a few papillary infoldings (Figs 1 and 2)

Two weeks later a laparotomy was performed At operation the uterus was the size of an eight week pregnancy Both appendages were normal No enlarged lymph nodes were present Total hysterectomy with bilateral salpingo-oophorectomy was carried out

At gross examination the uterus measured 11×9×4 cm The cavity contained a soft reddish mass measuring ?×1×1 cm attached to the fundus with few vesicular structures the diameter of which was up to 0 5 cm No embryonic structure was found

Microscopically in the cervix there were found foci of squamous metaplasia and mild dysplasia consisting of irregular stratification and epithelial cells with large hyperchromatic nuclei The soft mass with vascular structures present in the uterine fundus was a placenta with partial molar transformation Most of the chorionic villi showed receding vascularity or were avascular with an extensive oedema of the stroma and trophoblastic hyperplasia. Many chorionic villi were extremely enlarged and their stroma was acellular with hydropic degeneration Sheets of trophoblastic tissue composed of both syncytio- and cytotrophoblasts were found attached to the chorionic villi (Fig 3) No embryonic tissues were found microscopically Numerous trophoblastic cells were present in the decidual blood vessels The histopathological diagnosis after hysterectomy was Pregnant uterus with partial hydatidiform mole Granulation tissue with squamous metaplasia and mild dysplasia of cervix uteri

The patient made an uneventful recovery Two pregnancy tests in high dilutions on the eighth and ninth post-operative days were both negative After her discharge from hospital she had radiotherapy consisting by _000 r of Co[60] applied to the vaginal vault followed 2 weeks later by 3 800 r applied externally to her pelvis The second treatment was discontinued because of diarrhoea The woman remains well and is attending our follow up clinic All pregnancy tests were negative A chest X ray and intravenous pyelography performed in August 1974 were normal There is no evidence of any metastases She was last seen in August 1976 when her condition was excellent



Fig 1 Low power photomicrograph of well differentiated invasive cervical adenocarcinoma Hematoxylin-eosin

DISCUSSION

Adenocarcinoma of the cervix is found in 5% of all cervical malignancies (2 4) Interestingly enough while the incidence of carcinoma of the cervix is generally declining due to cervical cytology the proportion of adenocarcinoma appears to be increasing (9) Czernobilsky et al (3) found 7 cervical adenocarcinomas in a series of 60 Jewish women



Fig 2 High power view of cervical adenocarcinoma showing detail of histologic features Hematoxylin-eosin



Fig 3 Edematous avascular villi of partial hydatidiform mole Hematoxylin-eosin ×100

h cervical malignancies This incidence (11 7%) fers markedly from the general 5% incidence urring in non Jewish population

The incidence of carcinoma of cervix in preg ncy varies Dewhurst (4) stated that one in 5000 one in 20000 pregnancies is complicated by vical malignancy Kistner (6) in a review of 136 gnant women with cervical malignancy noted t about 1% of all cervical cancers occurred in gnant women and that pregnancy is complicated this disease once in every 2000 cases Of all cinomas found during pregnancy 3% are nocarcinomas (5 10) It seems that during the t 15 years with the wide and almost routine use cervical smears the statistical incidence of cinomas of the cervix in pregnancy has in ased (1) Most authors agree that there is no inite evidence that pregnancy has any deleteri l effect on the disease during the first and second nesters (6) Treatment of carcinoma of cervix in gnancy depends on the stage of pregnancy and degree of malignancy

The histological diagnosis of carcinoma in situ of vix in pregnancy is a rather difficult problem cause of the various changes in the cervical epi lium which are always present during pregnancy l which can give a false picture of malignancy e treatment therefore must be very cautious and rather conservative If a woman is young and desires more children she can continue with her pregnancy and have the cervix re-examined after confinement (6) Stage I and more advanced cer vical cancers found at the beginning of pregnancy necessitate termination of pregnancy to prevent spread of the disease But even if termination is not performed radiotherapy which is the treatment of choice is usually followed by spontaneous abor tion If the fetus is viable cesarean section is performed followed by radiotherapy There is a general 39% foetal wastage (11) Vaginal delivery should not be permitted and the abdominal route must always be preferred

The survival rate in cases treated in the first and second trimesters of pregnancy is almost similar to that of the non pregnant patients but becomes con siderably lower if treatment starts after the 32nd week of gestation or early puerperium (5 7) The importance of early diagnosis is therefore impera tive

We do not know the influence of hydatidiform mole on cervical malignancies as our case is the second reported in the medical literature We pre sume that the presence of chorionic gonadotrophin in high levels in the blood circulation as always happens in molar pregnancy has a possible stimulating effect on the cervical tumor

In our case in a grand multiparous Jewish woman an adenocarcinoma of the cervix uteri was diagnosed and at hysterectomy an unsuspected molar pregnancy was found. The adenocarcinoma was a polypoid mass which at the beginning of its development might have been a glandular polyp. The hormonal influence of the molar pregnancy with its marked trophoblastic hyperplasia could have been the trigger mechanism in the natural history of the transformation of a polyp into an adenocarcinoma although we have no proof that hormonal influences are directly involved in carcinogenesis in the cervix.

The dysplastic proliferation of the cervical epithelium found in the uterus removed two weeks after the complete excision of the adenocarcinoma might also have been influenced by the trophoblastic hyperactivity of the partial mole.

The post operative follow up for 4 5 years has been uneventful and X rays of chest spine and intravenous pyelography have been normal. We therefore presume that so far metastases can be ruled out.

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Submitted for publication Nov 19 1976

B Mazor
Department of Obstetrics and Gynecology
Carmel Hospital
Haifa
Israel

Acta Obstet Gynecol Scand 57 277–279 1978

OPERATIVE TREATMENT OF RECTAL ENDOMETRIOSIS

S Ruponen and E Taina

From the Department of Obstetrics and Gynaecology Turku University Central Hospital Turku Finland

stract 27 patients with rectal endometriosis were oper d upon in Turku University Central Hospital in 1976 The main symptom was defecation pain espe ly during menstruation Eighteen patients had had pre is surgery for endometriosis of the pelvic area A palp tumor was found on gynaecological examination in ry patient The tumors did not grow through the al wall Three kinds of operative procedures were lied (a simple excision method a so called window ration and resection of rectum) and the results were d

literature concerning this subject has so far n scarce Sampson (3) wrote his first case report years ago but surgical treatment at that time was ry risky The biggest series of rectal endo- triosis in recent years was published by Gray 1966 (?) In his article he also discussed surgical atment Many textbooks deal with the incidence this disease and suggest that endometriosis is nd in the rectum or the sigmoid colon in about 13% (Kaser Ikle) of all cases of endometriosis

MATERIAL AND METHODS

1969–1976 27 patients with rectal endometriosis were ited surgically in the Women s Clinic of Turku Uni sity Central Hospital Table I shows the age of the ients of whom 18 had had previous surgery for en metriosis The time between the first operation and the ration for rectal endometriosis was on average 32 nths During the first operation rectal endometriosis s found in 6 cases but in none of these was the rectal lometriosis treated surgically The patients had the ne kinds of symptoms as endometriosis patients gener / The symptoms are shown in Table II The main nplaint of the patient with rectal endometriosis is a inge in the bowel function during menstruation She has ier constipation or diarrhea but blood or mucus is not n in the stool In the 16 parous patients the average ie from the last pregnancy was 10 years On gynae logical examination a palpable tumor was found in the tovaginal space in every patient A barium enema s performed in 4 cases preoperatively and moidoscopy in 7 patients but the findings were normal

OPERATIVE TREATMENT

The operative procedures performed are found in Table III During the operation pelvic endometriosis was found in 24 patients and ovarian endometriosis in 22 patients The size of the tumors varied from 1×3 cm to 12×3 cm The tumors were at the sacrouterine level in 15 cases below the sacrouterine level in 3 cases above the level in 3 cases and extending from below to above the sacrouterine level in 3 cases Most often the tumor was located in the anterior wall of the rectum but in 6 cases the tumor extended around the wall to the dorsal side of the rectum

OPERATIVE TECHNIQUE

The patients were prepared preoperatively as follows The bowel was emptied and preoperative Neomycin® was given The surgical treatment was determined by the findings during the operation and a frozen section was obtained in every case to exclude malignancy In the excision operation the window that was made in the front wall of rectum was closed end to end in two layers using atraumatic plain catgut 00 in the first layer and plain catgut 0 in the second layer When endometriosis had extended to the dorsal side of the rectum the simple excision operation could not be performed In those cases we performed resection of rectum and the length of the resected area varied from 5 to 20 cm A so called pull through operation can also be done

Table I *Age distribution*

Age range	No of patients
21–25	?
26–30	4
31–35	10
36–40	8
41–45	2
46–50	1

Table 2

	Dysmenorrhea	Dys pareunia	Earlier operations for endo-metriosis
General symptoms	25	14	18
	Diarrhea	Obstipa tion	Defecation pain
Rectal symptoms	3 (during menstruation)	2	15
	2 (during inter menstrual period)	1	12

Number of patients 27

when rectal endometriosis is growing close to the anus We have often used this kind of operation in correction rectovaginal fistulas but so far we have not used this operation to treat rectal endometriosis Endometriosis found in other parts of the pelvic was treated as usual Bilateral oophorectomy had to be done in 2 cases because of severe ovarian endometriosis Hysterectomy was performed in 8 cases The size of the area excised from the rectum was decided by inspection and palpation At the end of the operation a careful lavage of the pelvis was performed with physiological saline solution and one dose of Hyalostop® (Leo) was instillated into the pelvic cavity

POSTOPERATIVE TREATMENT

ll the patients received antibiotics after the opera n either ampicillin intravenously or in the case f allergy cephalothin intravenously The antibiotic treatment was continued until the first defecation had occurred and at the same time parenteral nutrition was stopped We used no stimulation for the bowel function The average time to the first defecation was 4–5 days the shortest being 3 days and the longest 6 days after the operation

Postoperative fever occurred in 5 cases (over 38°C) The patients stayed in the hospital 8–14 days the average being 9–10 days In every case the histological diagnosis was rectal endometriosis

FINAL EXAMINATION

All the patients were examined in the hospital 2 months after the operation None had any rectal symptoms The troubles with the bowel [illegible] during menstruation had disappeared [illegible] no strictures of the rectum at the opera[illegible] Two cases had barium enemas and the [illegible] were normal

DISCUSSIO [illegible]

Rectal endometriosis is often associated [illegible] pelvic endometriosis In our material rectal en[illegible] metriosis was found alone in only one case [illegible] ally these patients have already been opera[illegible] for pelvic endometriosis and when symp[illegible] cur rectal endometriosis is sometimes found [illegible] change in the bowel function during menst[illegible] the main complaint The patient may have [illegible] constipation or diarrhea but the stool does [illegible] tain blood or mucus because endometrio[illegible] not grow through the rectal wall into the [illegible] This is why barium enemas and sigmoidos[illegible] not reveal this disease This is important [illegible] differential diagnosis of carcinoma of the r[illegible] tum Nevertheless the finding of a palpable [illegible] must always suggest the possibility of mal[illegible] Therefore operation for rectal endometriosis [illegible] only be performed in a hospital where there [illegible] facility for a frozen section This exam[illegible] should always be done A frozen sec[illegible] very useful to confirm the diagnosis of rectal en[illegible] dometriosis

Surgical treatment of rectal endometriosis [illegible] not be attempted if rectal endometriosis [illegible] covered unexpectedly in an unprepared pat[illegible] lateral oophorectomy will of course also lead [illegible] regression of rectal endometriosis On the [illegible] hand with careful preoperative management [illegible] good surgical technique and postoperative [illegible] rectal endometriosis can be cured [illegible] without doing bilateral ovariectomy at the [illegible] time The operation provides great satisfac[illegible]

Table 3

	Rectal procedures	Hys[illegible]
Excision of tumor (without penetrating rectal wall)	7	[illegible]
Excision of tumor (window method)	[illegible]	4
Resection of rectum	6	-
Pull through	[illegible]	
Bilateral ovariectomy	[illegible]	

patient because it effectively relieves defecation during menstruation The operator must have experience in intestinal surgery and therefore operation is not a routine gynaecological technique

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Submitted for publication May 9 1977

Seppo Ruponen
Department of Obstetrics and Gynecology
University Central Hospital
20520 Turku 52
Finland

TREATMENT OF MENOPAUSAL OESTROGEN DEFICIENCY SYMPTOMS IN HYSTERECTOMISED WOMEN BY MEANS OF 17β OESTRADIOL PELLET IMPLANTS

B Staland

From the Samariterhemmet Hospital Gynecological Outpatient Department Uppsala Sweden

stract Ninety four women having undergone hys rectomy with or without simultaneous ovariectomy re treated for menopausal symptoms by means of sub taneous implantation of sterile pellets containing 20 mg β-oestradiol 589 implantations in all The subjective ect was good and lasted generally for about 6 months e Karyopyknotic index serum FSH and plasma stradiol were checked in a few of the patients The thod was judged to be valuable in appropriate cases

β-oestradiol—the most important of oestrogens curring naturally in man—has long been used for eating menopausal symptoms in the form of ters for injection and in recent years for oral use esterified and free forms (1 3 4 6 8 10) The e of oestradiol in the form of pellets for sub taneous implantation is not new In particular fore long acting oestradiol esters for injection be ame available this method was used to a certain tent but only on a small scale There are only ief references to it in the literature The author as able to find only one more comprehensive udy—that of Muller (9) Chlonnda et al (2) tallworthy (13) Schleyer Saunders (11) and Studd 4) mention the method without giving details of e patient sample The patients in Muller s in estigation were mostly women with intact ombs According to present knowledge of estrogen treatment it is not surprising that bleeding ccurred fairly frequently The method is scarcely uitable for patients with uterus intact Even with mall amounts of oestrogens bleeding readily oc urs if the treatment is administered continuously or a long time Furthermore continuous oestrogen reatment may possibly predispose patients to en ometrial cancer The implantation method should herefore be reserved for women who have under one hysterectomy The author has used the method on such patients for more than 20 years The preparation used—Dimenformon compr ad implantationem (depot tablets)—was formerly re gistered in Sweden but over the last 10–15 years has been obtainable for licensed trial by courtesy of N/V Organon The sample discussed in this paper comprises all patients who have been accepted for treatment during the ten years from 1965 to 1975

METHOD

The preparation consists of compressed rod shaped pel lets containing 20 mg 17β-oestradiol without excipient The pellets measure 2 mm in diameter and are 6 mm long Each pellet is packed sterile in a vial Their shape makes it easy to implant the pellet subcutaneously using a trocar and cannula It also means that the surface area and there fore the absorption rate vary little during absorption period

Implantation is effected with a cannula with the same inside diameter as the diameter of the pellet implant (2 mm) and provided with two trocars—one pointed for in troducing the cannula and one blunt for inserting the pel let The implantations were effected subcutaneously in the lower abdominal wall The technique is extremely simple After a little local anaesthetic has been injected intra and subcutaneously a small incision 1–2 mm long is made through the skin with a pointed scalpel blade Through this the cannula with the pointed trocar is inserted 5–8 cm in the subcutaneous fat nearly parallel to the skin after which the implant pellet is inserted into the cannula and pushed in with the blunt trocar No suture is required With a little practice the whole procedure takes less than half a minute No visible scar is left Only at one single implantation did bleeding necessitate a suture Occasion ally minor insignificant haematomas have appeared but never any infection or other complication Any discomfort is insignificant and patients who have also had hormone injections report that the implantations are less unpleasant than injections When implanting in conjunction with laparotomy the pellet may be inserted from the operation incision with a pair of tweezers into the subcutaneous fatty tissue

Table I *Duration of the effect on climacteric symptoms*

Duration (months)	No of implant	% of implant with duration indicated (508)
0–4	2	0 4
4–5	19	3 7
5–6	104	20 5
6–7	254	50 0
7–8	49	9 7
8–	80	15 7
Undefined	81	
Total	589	100

PATIENTS

The series consist of 94 patients all of whom had undergone hysterectomy—in most cases total—including 46 with simultaneous bilateral ovariectomy For 15 of the patiens the first implantation was effected in conjunction with the operation for the others from less than 1 year to 29 years afterwards The ages at the start of treatment ranged from 38 to 72

The indications for treatment were in the first instance typical menopausal disorders in the form of sweating and hot flushes Less continuous symptoms such as headache palpitation muscular pains insomnia and various mental symptoms often occurred simultaneously In some older patients the symptoms of sweating and hot flushes were insignificant or completely absent The indication for treatment was here primarily urogenital symptoms such as vaginal atrophy with symptoms of so-called senile colpitis dysuria and urgency incontinence together with difficulties in resuming sexual relations Even in milder cases of stress incontinence the treatment was of some value

The series includes altogether 589 implantations The number of implantations in cases where the effect could be studied was between 2 and 38—for 61 patients at least 5 for 26 patients at least 10 implantations

RESULTS

The assessment of the effect was based primarily on information given by the patients themselves The subjective effect was very good throughout Only 2 patients reported an unsatisfactory effect on sweating and hot flushes Many patients had previously various forms of oestrogen treatment and practically all preferred the implantation method The patients also included an appreciable number who had previously been treated with sedatives and similar preparations without any effect whatsoever It is often stated that the placebo effect when treating menopausal symptoms is high Figures up to 35% have been indicated (5) This does not tally with the author s own experience nor wi[...] recent investigations Lauritzen (6) ind[...] ure of 10–13% The very poor effect of sed[...] itself constitutes evidence against a very [...] gree of placebo effect

No direct comparison with placebo [...] made in the present investigation though [...] forts in this direction were made howeve[...] when implantation was effected at the same [...] a bilateral ovariectomy the patients were [...] formed about implantation but were asked [...] if any climacteric symptoms appeared Th[...] tion of effect for this first implant is the same [...] for the patients as a whole The mean dura[...] implantation in conjunction with opera[...] 5 9±0 03 months For all cases together [...] 6 1±0 05 months Difference 0 2±0 3 mo[...]

Presumably the absorption time w[...] curtailed if the pellet was fragmented and [...] in fact observed when it was unint[...] broken during implantation This seemed to [...] chance to determine to what extent the [...] idea of the effective duration might be i[...] the check up being usually arranged for 6 [...] later In 21 cases selected at random the p[...] *deliberately broken into 2–3 pieces bef[...]* implanted This was not recorded in the [...] that the doctor should not unintentionally [...] patient when asking about the duration of th[...] The notes concerning fragmentation were [...] out until we went through the material for [...] ing it This showed as anticipated that t[...] *val before the disorders returned* was inde[...] er than usual It varied between 4 and 6 [...] with an average of 5 2±0 15 months compa[...] 6 1±0 05 months for the whole sample Th[...] ence was 0 9±0 16 months and theref[...] cally significant

Table I shows the duration of the subje[...] fect As a rule the patients were *treated* [...] 6 months This period was modified in [...] cases according to the duration of the ef[...] patients were requested to note the time of [...] sweating and flushes and were usually give[...] scription for some oral oestrogen prep[...] take when necessary Only in exceptional c[...] they need to avail themselves of this The [...] durations indicated in the table are to be reg[...] minimum ones as those patients who up[...] and further implantation had not always b[...] currence of symptoms at that time Th[...]

ɔle II *Objectı e parameters*

	Before treatment			3 months			6 months				
ermin	No	Varia tion	Mean	No	Varia tion	Mean	No	Varia tion	Mean	Months	Difference
%	6	0–10	2 0	6	35–66	46 1	6	10–40	18 5	0–3	44 1
										0–6	16 5
										3–6	−27 6
H l	5	6 7–15	10 5±1 7	10	0 4–9	3 7±1 0	16	0 5–14	4 1±0 8	0–3	6 8±2 0
										0–6	6 4±2 4
										3–6	0 4±1 3
pmol/l	3	37–9?	56 3±21 8	7	69–330	195 1±34 1	15	59–24?	152 5±14 7	0–3	138 8±40 5
										0–6	96 2±26 3
										3–6	42 6±37 1

t Test $p<0.05$ *t* Test $p<0.005$

ɔnths means at least 6 months but may exeed 7 ɔnths If symptoms had not recurred at two con utive implantations the time for check up was stponed by one month If there were no symp- ns even then the treatment was concluded to be sumed when necessary 0–4 months means at the effect had a duration of less than 4 months was incomplete The title undefined indicates ses where it was not possible to judge the effec e duration more accurately—chiefly patients th virtually only urogenital symptoms The table ows that in a large majority of cases a completely tisfactory effect was obtained for about half a ar Individual variation was rarely more than 1 onth except in cases with fragmentation of the llet On the other hand some patients consis ntly requested rather more frequent implantations an did others It is remarkable how accurately the tients could detect the time of return of the symp- ms as a rule within one or two weeks

In order to gain a more objective idea of the ormone effect objective parameters were used for naller groups of the sample Thus we studied the ryopyknotic index serum FSH and plasma stradiol Estimation of FSH and oestradiol was nerally performed 3 and 6 months after implanta on The results are given in Table II For 3 pa ents more detailed studies were carried out in con nction with the first implantation In these cases SH and oestradiol were determined immediately efore implantation and then after 1 week 2 weeks nd 1 3 5 6 and 7 months (Fig 1)

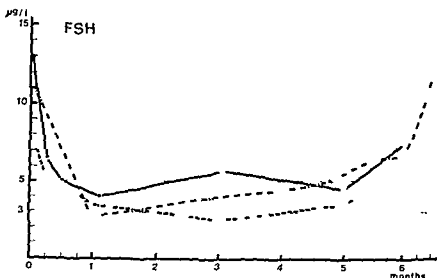
For 6 patients even at the first implantation the aryopyknotic index was determined before im lantation and again after 3 and 6 months (Table II)

As shown by Fig 1 the oestradiol levels rise and the FSH starts to fall within one week which tallies well with the patients own statements about the disappearance of the climacteric symptoms The levels then remain fairly constant for up to about 5 months By 6 months the levels have regained or begun to approach the original levels

Plasma oestradiol and serum FSH were de termined by radioimmunoassay (15) The upper limit for FSH in women of childbearing age is 3 μg/l Postmenopausally the values range from 5 μg/l upwards

The caryopyknotic index started to fall at 6 months but in none of the 6 cases studied was it as low at 6 months as at the beginning of treatment

The FSH and oestradiol values at 6 months had by no means always returned to the original levels The quickest to react is plasma oestradiol as is to be expected since this is the primary parameter It is also the one which best corresponds to the return of menopausal symptoms As a rule menopausal symptoms return when the plasma oestradiol falls below 100–120 pmol/l Serum FSH certainly gives a good idea of the effect of an oestrogen but need not necessarily drop despite a good effect of treatment This seldom occurs however and in fact did not do so for any of the patients studied in the present sample For one patient however the drop in FSH was appreciably less than usual 15 9 2 and 14 μg/l at 0 3 and 6 months respectively Despite this the effect was very good and the disorders had not returned after 6 months On the other hand the one and only patient whose plasma oestradiol did not reach 100 pmol/l after 3 months was one of the two cases where the effect was unsatisfactory Unfortu



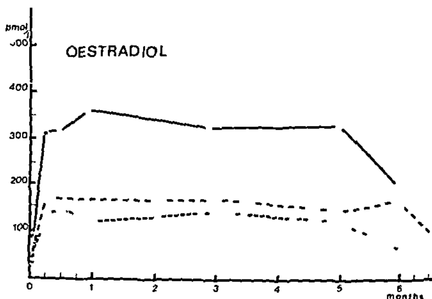


Fig 1 Serum FSH and plasma oestradiol after sub-cutaneous implantation of [illegible] mg 17β-oestradiol after the first implantation in 3 [illegible]

nately oestradiol determination was not carried out for the second of these patients

The appearance of the vaginal epithelium and the vaginal and—when cervix was left—the cervical secretion also showed a picture of strong oestrogenic influence

SIDE EFFECTS

Mastalgia was reported by 4 patients all over the age of 60 Only one of them regarded it as severe enough to want to switch to different treatment Otherwise no side effects were reported

Since all patients had undergone hysterectomy no bleeding could occur Likewise end[illegible] cancer does not of course come in o the p[illegible] There were no cases of mammary or [illegible] cancer nor of thrombosis In all the investig[illegible] covered approximately 300 patient years

Treatment was *discontinued* for 10 patients [illegible] one account of mastalgia (changeover to [illegible] oestrogen treatment) and in 2 due to lack of [illegible] In one of these the patient was switched [illegible] oestrogen injections in the other to high oral [illegible] of oestradiol Three patients stopped trea[illegible] because they felt that they no longer need[illegible] oestrogens and 4 changed over to oral treatment [illegible] practical grounds

DISCUSSION

most important of the natural oestrogens in —17β oestradiol— has proved to be extremely ful for treating menopausal symptoms both at l and parenteral administration With oral treat nt the doses must however be kept considera higher than for alkylated oestrogens e g inyloestradiol On the other hand many studies 3 6 7 16 etc) have demonstrated advantages npared with these chiefly as regards the effect blood lipids osteoporosis and the coagulation tem

The method described here—subcutaneous im ntation of 17β-oestradiol in the form of sterile lets—is not suitable as a general oestrogen atment because the absorption time is too long to w of the requisite breaks in the treatment at 1–2 nthly intervals However this does not seem ly to be a drawback for a patient whose uterus been removed In such circumstances the very g duration affords considerable advantages It is ually always possible to achieve a wholly sfactory effect with two implantations per an n The method is simple and is preferred by ny patients to other methods of administering trogens It is remarkable that such small ounts of oestrogen are required to keep the pa its free of symptoms With an effective duration 6 months the daily dose of oestradiol can be ulated to approximately 0 1 mg compared with ut 0 3 for injections of long acting oestradiol rs and at least 1 mg with oral administration of tradiol or oestradiol esters If the post nopausal endogenous production of oestradiol is koned at about 80 μg/24 h (12) the method uld afford a total amount of oestradiol of nearly μg/24 h which corresponds closely to normal trogen production in the years before the nopause (5) The relatively low but constant trogen level may be the reason for many patients ling that they feel better with the implantation atment than on oestrogens otherwise adminis ed The effect is nearly always complete whilst the other hand sign of too high oestrogen level h as mastalgia and oedema occur only in quite eptional cases

The disadvantage of course is that the method olves seeing a doctor However the time in ved in the treatment is very short The implanta n method seems to be particularly valuable in lateral ovariectomy We can thereby completely obviate the often very severe oestrogen defiency symptoms which are the immediate sequelae of the operation—an added strain in the postoperative condition of stress experienced by the patient

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Submitted for publication July 29 1977

Bertil Staland
Östra Ågatan 29
S 753 22 Uppsala
Sweden

Acta Obstet Gynec Scand 57 287–288 1978

SHORT COMMUNICATION

ABSORPTION OF A 8 HYDROXI QUINOLINE (STEROSAN®) THROUGH THE VAGINAL MUCOSA

Olav Meirik Karl Gosta Nygren Christina Fagerlund
and Per Hartvig

*From the Department of Obstetrics and Gynecology and the Department of Pharmacy
University Hospital Uppsala Sweden*

roquinaldol (5 7 dichloro 2 methyl 8 quino) in the form of vaginal jelly (Sterosan®) is ently used as an antibacterial and antimycotic t in gynecological praxis The active compo- is a compound of the 8 hydroxi-quinoline type ral of which have been made responsible for erious side effect usually known as subacute lo-opticus neuropathy (SMON) (6 7)

cently clioquinol another 8 hydroxiquinoline found to penetrate the human skin (2) In the ent study the absorption of chloroquinaldol ugh the vaginal mucosa is determined after the ication of one dose of vaginal jelly (Sterosan®)

SUBJECTS AND METHODS

e healthy regularly menstruating women applied at me a 5 g dosis of Sterosan® vaginal jelly (Geigy) con g 1% of chloroquinaldol Venous blood samples drawn at 0 1 3 6 12 24 and 48 hours The plasma separated and stored at −18 C until analysed

l urine was collected in 24 hours samples for three and stored as described above The stability of oquinaldol on storage has been verified (3)

e plasma concentration of chloroquinaldol was de med by electron capture gas chromatography after ctive methylation (3) Using a plasma volume of 0 5 own to 3 ng/ml could be detected

e urinary excretion was measured using 0 01–0 1 ml les The amount of chloroquinaldol excreted as con ed metabolites was determined after hydrolysis with curonidase at 37°C and pH=4–5 over night

RESULTS AND DISCUSSION

sma concentration of chloroquinaldol

oroquinaldol from vaginal jelly (Sterosan®) was nd to be readily absorbed from the vagina One r after application detectable amounts appeared lasma Mean plasma concentrations from the three women during 24 hours after administration are shown in Fig 1 Maximum concentration ap peared after 12 hours reaching a mean concentra tion of 16 ng/ml After that the concentration slowly declined and on the third day no chloroquinaldol could be detected in any of the three women

It has been shown that after oral administration of 300 mg of chloroquinaldol a peak plasma concentra tion of 7 μg/ml appeared after two hours (5) It must be pointed out that chloroquinaldol absorbed from the gut reaches the systemic circulation after partial detoxification in the liver After vaginal administra tion however the absorbed amount of chloro- quinaldol reaches the systemic circulation without being detoxificated

Urinary excretion of chloroquinaldol

Considerable amounts of chloroquinaldol appeared in the urine on the first and second day In two

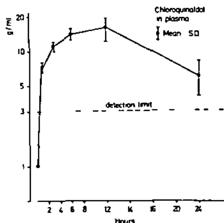


Fig 1 Mean plasma levels (±S D) of chloroquinaldol in three women after application of 5 g of vaginal jelly (Sterosan®)

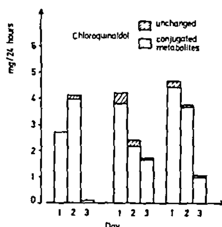


Fig 2 Urinary excretion of unchanged chloroquinaldol and conjugated metabolites in three women In the first urine specimen from the first woman only the amount of conjugated metabolites was measured

of the women detectable amounts were also found on the third day More than 90% of absorbed chloroquinaldol was excreted in urine as conjugated metabolites This is in accordance with findings with other 8 hydroxi quinolines (1 4) The total excretion in urine in the three women amounted to 14 15 and 18% respectively of the vaginal dose The daily excretion of unchanged chloroquinaldol and conjugated metabolites is shown in Fig 2

CONCLUSION

These results show that so-called local therapy with Sterosan® vaginal jelly results in the absorption of chloroquinaldol from the vagina into the [illegible] circulation This finding must be of [illegible] the assessment of side effects of this [illegible] larly for long term treatment and dur[illegible]

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Submitted for publication Dec 5 1977

Olav Meirik
Department of Obstetrics and Gynecology
University Hospital
S 750 14 Uppsala 14
Sweden

Acta Obstet Gynecol Scand 57 289–291 1978

CASE REPORT

HYPERVITAMINOSIS A IN EARLY HUMAN PREGNANCY AND MALFORMATIONS OF THE CENTRAL NERVOUS SYSTEM

Lars Stånge Kjell Carlstrom and Margareta Eriksson

From the Department of Obstetrics and Gynaecology Sabbatsberg Hospital Karolinska Institutet and the Department of Pediatrics St Goran Hospital Karolinska Institutet Stockholm Sweden

..act A case of malformations of the fetal central ..us system following hypervitaminosis A in early ..ancy is reported The mother was treated with ..00 IU vitamin A daily during gestation days 19 to 40 ..mination of urinary oestriol carried out in the 42nd .. of pregnancy revealed a very low excretion (4 ?–6 6 ../24 h) Induced delivery resulted in a microcephalic ..who died after 18 min The child had multiple ..rmations of the central nervous system and very .. adrenal glands (1 5 g normal 11±4 g) The very low ..ry oestriol excretion is well explained by the hypo-..c adrenals which in turn can be related to insuffi.. ACTH stimulation a condition similar to anencepha.. ..he malformations shown in the present case are con..ed to be related to the high doses of vitamin A given .. mother and the authors wish to warn against uncrit..use of high doses of vitamin A in women of childbear..ge

..rvitaminosis A has been known to be ..ogenic in experimental animals since 1953 ..1 it was shown to induce congenital anomalies ..ts (2) Since then numerous studies in different ..al species have confirmed these results (14) ..ral types of malformations have been reported ..ng them anomalies of the central nervous ..m (1? 15)

..humans the teratogenic potential of excessive ..e of vitamin A has been discussed (5 10 15) ..ever only two case reports exist so far which ..ent a possible relationship between hypervita..osis A and malformations in humans (1 12) In ..the reported cases the infants were born with ..enital abnormalities after maternal intake of ..00 and 40 000 units of vitamin A daily during the ..cal period

..itamin A has recently found a new therapeutic ..ication for treatment of acne (7) The present communication describes a case in which the mother was treated with high doses of vitamin A during early pregnancy for this condition She showed a very low urinary oestriol excretion during later stages of pregnancy and gave birth to a child with malformations of the central nervous system who died shortly after delivery

METHODS

Urinary oestriol excretion

The excretion of oestriol in the maternal urine was determined by the method of Frandsen (3)

Determination of placental steroid sulphatase activity

Rapid determination of the placental steroid sulphatase was carried out by the following technique 1 2 g of frozen placental tissue was thawed washed with 0 06 M Tris-HCl pH 7 ? and homogenized for 60 sec with 5 ml of this medium in an Elvehjem Potter homogenizer at +4 The homogenate was centrifuged at 6 000 rpm for 10 min and the supernatant was collected

The assay mixture consisted of 0 4 ml diluted placental homogenate or 0 4 ml Tris buffer control and 745 cpm [4- C]dehydroepiandrosterone sulphate (specific activity 55 0 Ci/mol) in 7 μl of ethanol The samples were incubated at 37°C for 15 min All incubations were carried out in duplicate After that 0 2 ml of 0 5 M sodium phosphate buffer pH 7 5 was added and the liberated [4-^{14}C]-dehydroepiandrosterone was extracted with 1 ml of toluene After centrifugation the toluene layer was taken to liquid scintillation counting of the ^{14}C radioactivity Protein concentration in the placental homogenates was determined by the biuret method (9)

CASE REPORT

The mother was aged 26 years healthy and pregnant for the second time with normal delivery of a healthy child 3 years earlier In early pregnancy the mother visited a

Table I *Urinary oestriol excretion (μmol/24 h) and placental sulphatase activity* (pmol liber[illegible] dehydroepiandrosterone ×(mg protein)⁻¹×(min)⁻¹

	Hyper vitaminosis A patient	Placental sulphatase deficiency	Normal control case	Reference values 38th to 42nd week of pregnancy
Urinary oestriol excretion days before delivery				
4		7 9	124	
3	6 6		112	36–198
2	4 2		143	
1		4 8	170	
Delivery at week	42	38	38	-
Placental sulphatase activity	66	3 0	146 0	-

dermatologist because of acne and was prescribed a vitamin A preparation (Ido A®) 50 000 units three times daily *She took this from gestation day 19 to day 40* when she stopped becuase she realized that she was pregnant The rest of the pregnancy was normal until the expected delivery day When the patient was still not delivered 10 days after term determination of the urinary oestriol excretion was carried out revealing very low excretion values (Table I)

X ray examination showed a considerably smaller head than would be expected in relation to the fetal body The fetus seemed to be microcephalic and therefore delivery was induced by amniotomy and oxytocin infusion After 5 *hours of labour a 3 100 g baby was born that was obviously* microcephalic It died after 18 min

The autopsy revealed a brain (weight 130 g) that was macerated with considerable amounts of blood in the skull cavity The ventricles were grossly dilated and the parenchyma of the cerebrum was only 1 cm thick Between the third and fourth ventricles there was a stricture of the aqueduct The cerebellum was not pathologically affected The kidneys were hypoplastic together weighing [illegible]ly 0 5 g The adrenal glands were small (1 5 g normal 11±4 g) The circulatory respiratory and digestive organs were normal otherwise

The placenta (530 g) was without pathological changes In order to exclude a placental steroid sulphatase deficiency as a possible cause to the low maternal urinary oestriol values *the placental sulphatase activity was de*termined The sulphatase activity was found to be in the same magnitude as in a normal control subject and far higher than in the case of placental sulphatase deficiency (Table I)

DISCUSSION

The development of the gross morphology of the brain takes place in the 3rd to 5th week of fetal life i e when this mother was treated with high doses of vitamin A Hypervitaminosis A has been discussed as a possible pathogenic mechanism f[illegible] malformations of the central nervous sys[illegible] such malformations can be induced in a[illegible] administration of vitamin A (6) It has a[illegible] observed that higher postpartum maternal levels of vitamin A were present following the [illegible] of infants with CNS malformations tha[illegible] the birth of healthy babies (5) In the two [illegible] reported cases with a possible relationship be[illegible] intake of vitamin A and birth of a malf[illegible] malformations of the urogenital tract was [illegible] 12)

The low maternal urinary oestriol [illegible] well explained by the severely hypopl[illegible] nals a condition similar to that found [illegible] (4) and which is considered to relate to [illegible] cient *ACTH* stimulation

It has been reported by Piziak and Co[illegible] that vitamin A greatly increases the [illegible] of progesterone in guinea pig placenta [illegible] analogous effect on the correspondin[illegible] zymes might cause an increased [illegible] other 20-oxosteroids such as 5-pregn[illegible] its sulphate and this in turn might interfere [illegible] transformation of these steroids in [illegible] oestrogen precursors dehydroepiandro[illegible] dehydroepiandrosterone sulphate It has [illegible] reported by Nakamura (11) that excess [illegible] decreases the uptake of inorgani[illegible] sulph[illegible] formation of chondroitin sulphate [illegible] might speculate over an analogous effect [illegible] sulphurylation of Δ^5 3 β hydroxy [illegible] terfering with the transforma[illegible] of the[illegible] into oestriol However these [illegible] less likely A placental sulphatase defic[illegible]

out by the sulphatase activity figures given in :I

e dose in-gested by the mothers described in ·I and I? were 25 000 and 40 000 units respec ' In the present case the mother took 150 000 daily during the critical period The recom led daily allowance for vitamin A during preg y is 5000 units an increase of 25% over the 'ance for the nonpregnant adult female (13) reatment of acne a dose of 100 000 units daily been recommended (7) Since acne is a com condition during childbearing age we wanted port this case with a possible relationship be n hypervitaminosis A and later birth of a ormed child to warn against uncritical use of doses of vitamin A in women of childbearing

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Submitted for publication Jan 14 1977

Lars Stånge
Department of Obstetri s and Gynecology
Sabbatsberg Hospital
113 82 Stockholm
Sweden

ANNOUNCEMENTS

During the 6th European Congress of Perinatal Medicine held in Vienna Austria from August 30 to September 1 1978 the *Maternitee Prize* of the European Society for Perinatal Medicine will be awarded for outstanding experimental clinical and organizational achievements in the field of Perinatal Medicine President s address Prof Dr O Thalhammer Univ Kinderklinik Wahringer Gurtel 74 A 1090 Wien Austria

The Second World Federation of Nuclear Medicine and Biology Meeting will be held in Washington D C USA September 17–21 1978 For further information write to Administrative Secretariat Second International Congress of Nuclear Medicine and Biology Suite 700 1629 K Street N W Washington D C 20006 USA

International Society for Cryosurgery Organized in 1974 the *International society for Cryosurgery* was established to foster the continued development and application of cryosurgery for the controlled cryogenic [illegible] abnormal tissues

An integral part of this development and [illegible] not only in advances in instrumentation and [illegible] of technique toward attainment of improved [illegible] clinical palliation and treatment but in [illegible] edge of the biochemical physiological [illegible] morphological alterations following freezing.

Presently the *Society* holds an International C[illegible] every third year where the latest results in [illegible] plines are presented and discussed State of the [illegible] round tables in which leading authorities [illegible] *Society* has been a major feature at the congresses.

The *Society* welcomes applications for member[illegible] from individuals whose qualifications and interest [illegible] been demonstrated by experience and publication [illegible] relevant field Applications for membership may be [illegible] tained from the *Society s* Secretary Dr Mario [illegible] Via Nizza 39 10125 Torino Italy Annual dues [illegible] Successful applicants will be billed following [illegible] membership

Acta Obstet Gynecol Scand 57 293–300 1978

OVARIAN FOLLICULAR APPARATUS AND HORMONAL PARAMETERS IN PATIENTS WITH PRIMARY AND SECONDARY AMENORRHEA

Ryosuke Nakano Nobuyuki Hashiba Motoo Washio and Shimpei Tojo

From the Department of Obstetrics and Gynecology Kobe University School of Medicine Kobe Japan

tract Correlation between ovarian follicular apparatus and hormonal parameters such as serum gonadotropin and urinary estrogen levels was investigated in patients with primary and secondary amenorrhea. Serum gonadotropin levels were elevated in amenorrheic patients without ovarian follicles or with follicles of low developmental stage and pituitary responsiveness to LH-RH in these patients were marked compared with patients with follicles of high developmental stage or normal ovulating women in the follicular phase of the menstrual cycle. The 24-hour urinary excretion of total estrogens was low in patients without follicles or with follicles of low developmental stage and ovarian responsiveness to exogenous gonadotropins was quite low in comparison with patients with highly developed follicles and normal control subjects. Thus serum gonadotropin and urinary estrogen measurements and LH-RH and gonadotropin loading tests are diagnostic of the presence or absence and the state of development of ovarian follicles in the diagnosis and treatment of primary and secondary amenorrhea

In the diagnosis and treatment of amenorrhea histologic finding of the ovary especially knowledge of the presence or absence of ovarian follicular tissue is of paramount importance and ovarian biopsy either by laparotomy laparoscopy or culdoscopy is an accepted procedure for making the histologic assessment. Although efforts have been made by several investigators to associate hormonal parameters such as urinary or plasma gonadotropin levels with the presence or absence of ovarian follicles correlation has not been sufficiently demonstrated (12 13 14)

In 1973 Goldenberg et al (6) re examined the possibility of obtaining the necessary diagnostic information indirectly by correlating the presence or absence of ovarian follicular tissue with measurements of urinary gonadotropins and plasma luteinizing hormone (LH) and follicle stimulating hormone (FSH) values in patients with primary and secondary amenorrhea. They reported that a single plasma FSH value was found sufficient to diagnose the presence or absence of ovarian follicles in every amenorrheic patient

The present paper is of the correlation between the state of ovarian follicular apparatus and hormonal parameters such as serum LH and FSH levels and the 24-hour urinary excretion of total estrogens in patients with primary and secondary amenorrhea

MATERIALS AND METHODS

41 amenorrheic patients were studied. Twenty patients had primary amenorrhea and twenty-one patients had secondary amenorrhea. Ovarian biopsy was performed in the diagnostic evaluation of these amenorrheic patients. Specimens were fixed sectioned and stained with hematoxylin and eosin and evaluated microscopically for absence (Fig 1) or presence (Figs 2 and 3) of ovarian follicles. The cases with follicles were further classified into two groups cases with (1) follicles of low developmental stage (primordial–secondary follicle) (Fig) and ( ) follicles of high developmental stage (tertiary–Graafian follicle) (Fig 3)

The patients were grouped on the basis of primary and/or secondary amenorrhea absence or presence of follicles developmental stage of follicles and the etiologic diagnosis of the disorder (Table I)

Eleven normal female volunteers whose ages ranged from 24 to 30 years served as controls. All the women had regular ovulatory menstrual cycles with intervals between periods from 8 to 3? days. The subjects were studied during the follicular phase of the menstrual cycle (cycle day 7). Determinations of the follicular phase of the cycle was based on (1) knowledge of the length of five or more of the most recent consecutive menstrual cycles (2) daily basal body temperature readings and (3) the timing of the subsequent menstrual cycle

Serum LH and FSH levels were measured in duplicate by a double antibody radioimmunoassay utilizing reagents provided by the Human Pituitary Program of the National Institute of Arthritis Metabolism and Digestive Diseases according to the method of Odell et al (11) and Midgley (7) with modifications. Both Second International Reference Preparation of Human Menopausal Gonadotropin



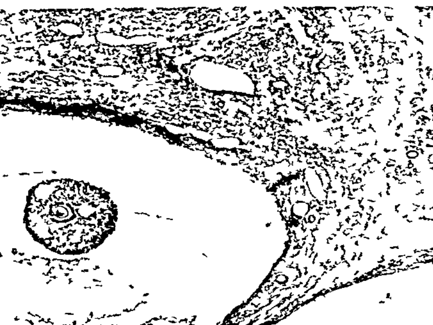
Fig 1 Ovary of an amenorrheic patient without ovarian follicles Streak ovary with fibrous tissue in the syndrome of gonadal dysgenesis (H&E ×70)

(2nd IRP-HMG) and LER 907 were used to obtain standard curves The average relative potencies of these preparations were 304 IU of 2nd IRP-HMG/mg LET 907 for LH and 44 IU of 2nd IRP-HMG/mg LER 907 for FSH The results of this study were expressed as mIU of 2nd IRP-HMG/ml of serum Total urinary [illegible] measured in 24 hour samples according to the [illegible] Brown et al (2)

Normal control subjects and amenorrheic [illegible] each subjected to a luteinizing hormone rele[illegible]



Fig 2 Ovary of an amenorrheic patient with ovarian follicles at an early developmental stage Numerous unstimulated primordial follicles and [illegible] follicles up to the antral stage (H&E ×[illegible])

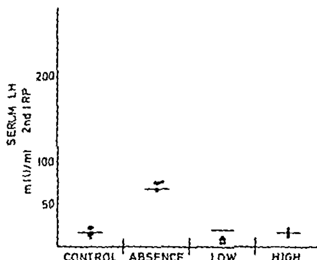


3 Ovary of an amenorrheic patient with ovarian icles at a late developmental stage Advanced tertiary follicle surrounded by an active ovarian stroma (H&E × 8)

ne (LH-RH) loading test and a gonadotropin load test in order to test pituitary and ovarian responsive s The synthetic LH-RH used in this study was syn sized and generously supplied by Daiichi Seiyaku Co d Tokyo Blood was sampled at time zero and at 15 45 60 and 1 0 min for determination of serum LH and H A gonadotropin loading test was performed accord to the following schedule and the ovarian response s evaluated by daily estimation of the 24 hour urinary excretion of total estrogens The human menopausal gonadotropin (HMG) used was Humegon (Organon Amsterdam the Netherlands) Each ampule contained 75 IU (nd IRP-HMG) of FSH activity and 44 IU (2nd IRP-HMG) of LH activity The human chorionic gonadotropin (HCG) was generously supplied by Teikoku Hormone Tokyo and its activity was calibrated against Second International Standard of Human Chorionic Gonadotropin (2nd IS-HCG) HMG (150 IU) and HCG

ble I *Distribution of patients with primary and secondary amenorrhea with absence or presence of arian follicles according to their probable diagnosis*

	Primary amenorrhea			Secondary amenorrhea	
	Absence of follicles		1	Absence of follicle	
	Turner s syndrome	4			0
	Gonadal dysgenesis with normal karyotype	6			
	Presence of follicles		2	Presence of follicles	
	Early developmental stage (Primordial-secondary follicle)		(i)	Early developmental stage (Primordial-secondary folli le)	
	Primary ovarian failure (Atrophic or hypoplastic ovary)	3		Premature menopause	4
	Unknown etiology	3		Unknown etiology	1
i)	Late developmental stage (Tertiary-Graafian follicle)		(ii)	Late developmental stage (Tertiary-Graafian follicle)	
	Primary ovarian failure (Atrophic or hypoplastic ovary)	-		Pituitary Adenoma	
	Unknown etiology	2		Sheehan s syndrome	1
				Forbes Albright syndrome	1
				Premature menopause	1
				Polycystic ovary syndrome	5
				Unknown etiology	6
	Total	20		Total	21



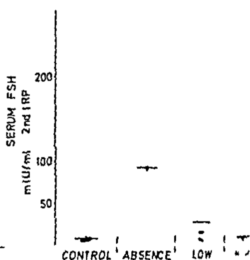


Fig 4 Serum LH and FSH levels in patients with primary amenorrhea without ovarian follicles (*absence*) and with follicles at an early (*low*) or late (*high*) developmental stage compared with those in normal ovulating [illegible] the follicular phase (*control*)

(3000 IU) were administered by intramuscular injection on the 1st and 3rd days of the gonadotropin loading test and total urinary estrogens were measured for five consecutive days

Informed consent was obtained from each subject after the purpose and nature of the study had been fully explained

Statistical significance of the data was tested at the 0 05 and 0 01 levels by Student s *t* test

RESULTS

Serum LH and FSH levels in ten patients with primary amenorrhea without ovarian follicles were higher than those seen in normal ovulating women in the follicular phase of the menstrual cycle $p < 0\ 01$) In contrast serum gonadotropin levels in patients with follicles were similar to those in [illegible]al control subjects (Fig 4)

The twenty one patients with secondary amenorrhea had ovarian follicles eithe [illegible] developmental stage (primord [illegible]-secondary [illegible] or at a late developmental stage (tertiary-[illegible] follicle) Serum LH and FSH levels in [illegible] with follicles at an early developmental [illegible] elevated compared with normal women in the [illegible]licular phase ($p < 0\ 01$) On the other hand [illegible] gonadotropin levels in patients with fo[illegible] late developmental stage did not differ [illegible] from those in normal control subjects (Fig [illegible]

The 24 hour urinary excretion of [illegible]gens in patients with primary amenorrhea [illegible] ovarian follicles or with follicles at an ea[illegible]velopmental stage was lower than that in [illegible] subjects in the follicular phase ($p < 0\ 01$ [illegible] respectively) Urinary excretion of estrogen [illegible]tients with follicles at a late developmental [illegible] not differ from that in control subjects (Fig [illegible]

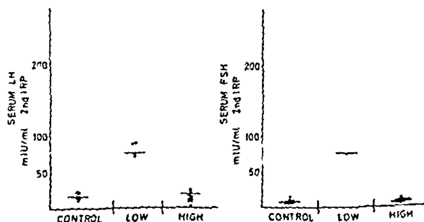
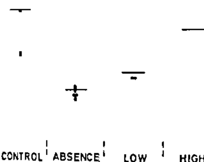


Fig 5 Serum LH and FSH levels in patients with [illegible] amenorrhea with ovarian [illegible]cles of early (*low*) or [illegible] developmental stage [illegible] with those in normal ovulating women in the follicular phase (*control*)



The 24-hour urinary excretion of total estrogens in with primary amenorrhea without ovarian folli and with follicles at an early (*low*) or late opmental stage compared with that in normal ng women in the follicular phase (*control*)

y estrogen levels in four patients with sec r amenorrhea with follicles at an early de l stage were lower than those in normal in the follicular phase ($p<0.05$) Seven nts with follicles at a late developmental showed approximately the same estrogen in urine compared with normal control sub g 7)

effect of synthetic LH-RH on serum LH and vels in normal ovulating women in the fol phase is illustrated in Fig 8 Synthetic

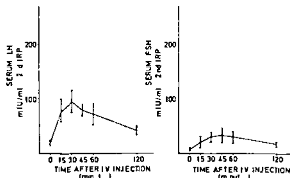


Fig 8 The effect of synthetic LH-RH on serum LH and FSH levels in normal ovulating women in the follicular phase Bars indicate S E

LH-RH stimulated a concomitant release of LH and FSH in these subjects

Synthetic LH-RH evoked a marked release of LH and FSH in patients with primary amenorrhea without ovarian follicles compared with normal control subjects In contrast LH and FSH response to LH-RH in most patients with follicles was approximately analogous to that seen in normal women in the follicular phase Only one patient with follicles at an early developmental stage showed a marked response to LH-RH (Fig 9)

Serum LH response to LH-RH in patients with secondary amenorrhea with follicles at an early developmental stage was higher than that in control subjects Although LH response to LH-RH in most patients with follicles at a late developmental stage



The 24 hour urinary excretion of total estrogens in with secondary amenorrhea with ovarian follicles (lo) or late (*high*) developmental stage com with that in normal ovulating women in the follicular (*control*)

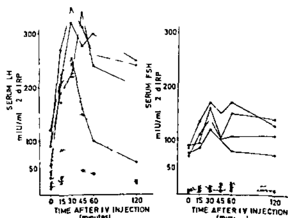


Fig 9 The effect of synthetic LH-RH on serum LH and FSH levels in patients with primary amenorrhea without ovarian follicles (O—O) and with follicles at an early (●—●) or late (● ●) developmental stage

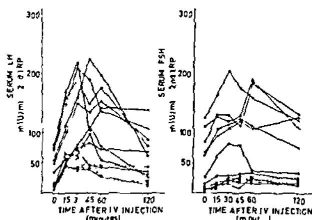


Fig 10 The effect of synthetic LH-RH on *serum LH and FSH* levels in patients with secondary amenorrhea with ovarian follicles at an early (●—●) or late (● ●) developmental stage

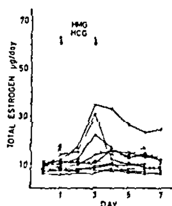


Fig 12 The ovarian response to exogenously administered HMG and HCG on day 1 and 3 of the gonadotropin loading test in patients with primary amenorrhea without ovarian follicles (O—O) and with follicles at an early (●—●) or late (● ●) developmental stage

was similar to that seen in normal women LH response in five patients with polycystic ovary syndrome was extraordinarily high and response in *one patient* with *Sheedan s* syndrome was subnormal Serum *FSH response to LH-RH* in patients with secondary amenorrhea showed a marked contrast FSH response in patients with follicles at an early developmental stage was high but response in patients with follicles at a late developmental stage was similar to that seen in normal women in the follicular phase of the menstrual cycle (Fig 10)

The ovarian response to exogenously administered *HMG* and *HCG* on cycle day 5 and 7 in eleven normal ovulating women in the follicular phase was shown in Fig 11 All the subjects responded to exogenous gonadotropins with a rise in the 24 hour urinary excretion of total estrogens

The gonadotropin loading test was carried out in the same manner in thirteen patients with primary amenorrhea and nineteen patients with secondary amenorrhea No ovarian response was observed in five patients with primary amenorrhea without ovarian follicles About half of the eight patients with follicles at early or late developmental stage were responsive to HMG and HCG (Fig 12)

Although five patients with secondary amenorrhea with ovarian follicles at an early developmental stage did not respond to HMG and

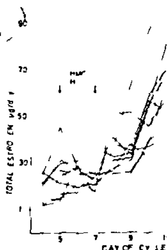


Fig 11 The ovarian response to exogenously administered HMG and HCG on cycle day 5 and 7 in normal ovulating women in the follicular phase

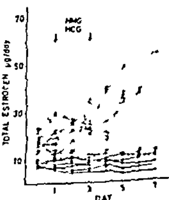


Fig 13 The ovarian response to exogenously administered HMG and HCG on day 1 and 3 of the gonadotropin loading test in patients with secondary amenorrhea with ovarian follicles at an early (● ●) or late (● ●) developmental stage

; eleven of the fourteen patients with follicles lage developmental stage responded with a nse in urinary excretion of total estrogens 13)

DISCUSSION

ılogic findings of the ovary especially ledge of the absence or presence of ovarian ular apparatus and of the state of follicular opment is quite important in the diagnosis and nent of primary and secondary amenorrhea y of the ovary for the assessment of orrhea has been advocated as part of the clini nvestigation (5 15 17 18) Histologic study of iopsies was made with particular reference to ollicular tissue and a correlation was shown en the state of the follicular apparatus and the quent clinical progress (20) Provided some ular element can be seen in the ovary success nduction of ovulation would be expected ulation would be however persistent and un onsive to stimulant treatment in amenorrheic nts where no follicular tissue can be found on logic examination

ı the other hand it is generally accepted that varian biopsy is not always free from hazards Thus attempts have been made to associate crine parameters such as serum gonadotropin or steroid hormone levels with the ovarian phology with special reference to the follicu lement but correlation has often not been iently demonstrated (12 13 14) In 1973 enberg et al (6) measured total urinary dotropins plasma LH and FSH in normal en and in patients with primary and secondary norrhea and respectively correlated with the nce or absence of ovarian follicles According eir results total urinary gonadotropin levels LH values were greater in patients follicles than in patients with follicles and women but the degree of overlap prohibited diagnosis in any individual patients Only a FSH value reliably predicted the presence ence of ovarian follicular element in women ither primary or secondary amenorrhea his series serum LH and FSH measurements upon a reliable radioimmunoassay was dia tic of the presence or absence of follicles in nts with primary amenorrhea and also dia ic of the state of development of follicles in s with secondary amenorrhea The 24 hour urinary excretion of total estrogens was signifi cantly lower in patients with primary amenorrhea without ovarian follicles or with follicles at an early developmental stage and in patients with sec ondary amenorrhea with follicles at an early de velopmental stage Thus total urinary estrogen values also have diagnostic significance concerning knowledge of the presence or absence and the de velopmental stage of ovarian follicular apparatus

Synthetic LH–RH has proved to be an effective means of testing the pituitary secretory reserve for LH and FSH Pituitary responsiveness to LH–RH in patients with hypogonadism has been reported by several investigators (1 8 9 23 24) It is reported that gonadotropin response to LH–RH in ovarian hypogonadism is significantly higher and response in pituitary hypogonadism is lower than that in the follicular preovulatory and luteal phases of the menstrual cycle However little is known about the correlation between the state of follicular growth and the responsiveness to LH–RH The results of the present study suggest that LH and FSH re sponse to LH–RH is high in amenorrheic patients without ovarian follicles or with follicles at an early developmental stage and moderate or low in pa tients with follicles at a late developmental stage

The ovarian responsiveness to exogenously ad ministered gonadotropins has been reported by several investigators (3 4 10 16 21 22) These results indicate that ovarian refractoriness to gonadotropins suggests ovarian failure and ovarian responsiveness suggests hypothalamic ovarian fail ure In the present study the ovaries with follicles at a late developmental stage responded sufficiently to exogenous gonadotropins whereas most of the ovaries without follicles or with follicles at an early developmental stage did not The ovarian response to exogenous gonadotropins is considered to be closely correlated with the presence or absence and the developmental stage of follicular element

Studies on correlation between ovarian mor phology and hormonal parameters are of im portance in the diagnosis and treatment of primary and secondary amenorrhea and further studies are needed

ACKNOWLEDGEMENTS

We acknowledge the generous supply of materials for radioimmunoassay of human pituitary gonadotropins by the Human Pituitary Program of the National Institute of Arthritis Metabolism and Digestive Diseases The Sec

ond International Reference Preparation of Human Menopausal Gonadotropin was obtained from the National Institute for Medical Research

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Submitted for publication Aug 16 1977

Ryosuke Nakano
Department of Obstetrics and Gynecology
Kobe University School of Medicine
Kobe Hyogo 650 Japan

Acta Obstet Gynecol Scand 57 301–311 1978

OVARIAN BIOPSY IN THE EVALUATION OF AMENORRHEA

Karam Karam and Adnan Mroueh

From the Department of Obstetrics and Gynecology American University Hospital Beirut Lebanon

act Endoscopic ovarian biopsies were performed on nenorrheic patients in an attempt to determine the gy of their amenorrhea and predict its prognosis lating the histologic examination with physical find endocrine patterns and cytogenetic studies Ovarian les were present while gonadotropins were high in 14 s (6 primary 8 secondary) and there were no follicles ases (3 primary 1 secondary) whose gonadotropins low Secondary sex characteristics were well de ed without prior estrogen stimulation in 5 cases of ary amenorrhea who had no follicles and whose dotropins were either low 3 or high ? The mere nce of ovarian follicles was not enough to make them onsive to gonadotropin stimulation whether endoge or exogenous a phenomenon that had to do with the ty and quantity of germinal follicles available The logic examination of ovarian tissue for the evaluation nenorrhea has been made feasible and relatively safe igh recent advances in endoscopic techniques

norrhea is a symptom of wide variety of dis rs whose evaluation and treatment largely de d on a clear knowledge of ovarian function For assessment we generally rely on indirect hods like physical examination gynecography oid assay gonadotropin output and chromo- e studies Though helpful yet these indices may to reflect the exact status of the ovaries owledge of ovarian histology although very in tive has not been utilized fully because of the bidity and expense incurred in laparatomies of nan biopsies Laparatomy was considered only n a disparity between clinical findings and oratory investigation existed (14)

ecently there has been a resurgence of interest oth diagnostic and operative endoscopy This been due to advances in technology instrumen on and refinements in culdoscopic and laparo- nic techniques Operative procedures have been ne through the culdoscope as early as 1963 when man introduced his panculdoscope (2) Marshall Hammond (5) reported on 25 ovarian biopsies performed under culdoscopic visualization with only minimal patient morbidity Steele and associates (17) recommended laparoscopic ovarian biopsy in the investigation of amenorrhea reporting 28 cases they have studied For some the inadequacy of indirect methods to assess gonadal function was not sufficient to obviate a diagnostic surgical procedure with its associated risks (10 11 12 13 18) For others a single plasma FSH value was found sufficient to diagnose the presence or absence of ovarian follicles (3) This report is to describe outpatient ovarian biopsies performed by culdoscopy or laparoscopy on 78 amenorrheic patients in an effort to evaluate their amenorrhea

METHODS AND MATERIALS

From September 1 1971 to Septemtber 1 1975 the authors have performed 78 ovarian biopsies on women with primary 35 and secondary 43 amenorrhea chosen from the reproductive endocrinology clinics of the American University Medical Center The diagnostic workup prior to endoscopy included a complete medical history and physical examintion routine urinalysis hematological studies and vaginal cytology

Radiological examinations of the sella turcica as well as visual fields were performed on all cases with secondary amenorrhea and most of the primary amenorrhea cases

Total urinary gonadotropins were determined by bioassay in 36 patients using the method described by Brown (1) and expressed in Mouse uterine units LH urinary levels were occasionally estimated by luteonosticon immunochemical test supplied by Organon using the ?nd IRP HMG as the standard with values expressed as International units in 24 hour urine with normal ovulatory levels of 150–500 IU/24 hr Serum gonadotropins FSH and LH were measured on 42 cases by double antibody radioimmunoassay procedures (6 7) and all samples were performed in the same assay in duplicate The Second International Reference Preparation of human menopausal Gonadotropin was used as a reference standard for both the FSH and LH assays and expressed in M I U second IRP HMG per milliliter with normal follicular phase levels of 5 to 15 MIU/ml for each Endocrine tests

Table 1 *Gonadotropins and ovarian histology in 35 women with primary amenorrhea*

Pat no	Gonadotropins	Gross appearance	Ovarian biopsy
Normal sexual development			
1	Pos 6 12 24 M U	Small Thick capsule	Luteinized stroma Germinal follicles Cystic follicles Thick capsule
2	Pos 6 12 24 48 M U	Small	Normal stroma Germinal follicles Old corpus luteum
3	Pos 6 12 24 M U	Small	Normal stroma Germinal follicles Graafian follicles Corpus albicans
4	Pos 6 12 24 M U	Small	Normal stroma Germinal follicles Graafian follicles
5	Pos 6 12 M U	Small	Normal stroma Germinal follicles
6	Pos 6 12 24 M U	Streak	Normal stroma Few germinal follicles
7	5IU/24hrs	Streak LT Cystic mass RT	LT normal stroma Few germinal follicles RT benign cystic teratoma
8	FSH 1 5 MIU/ml LH 2 MIU/ml	Streak	Normal stroma Germinal follicles
9	Neg 6 M U	Small	Normal stroma Germinal follicles Degenerating graafian folli-cles
10	Pos 6 M U	Small	Normal stroma Germinal follicles
11	Pos 6 M U	Small	Normal stroma Germinal follicles
12	Neg 6 M U	Small	Normal stroma germinal and graafian follicles undergoing atresia
[illegible]	FSH 5 25 MIU/ml *LH 7 5 MIU/ml*	Small	Normal stroma Germinal follicles
14	FSH 2 MIU/ml LH 2 MIU/ml	Small	Normal stroma Germinal follicles
15	FSH 10 MIU/ml	Small	Normal stroma Germinal follicles
16	Neg 6 M U	Small Cystic	Normal stroma Germinal follicles Few cystic follicles
17	FSH 2.5 MIU/ml LH 2.1 MIU/ml	Small cystic Thick capsule	Stromal fibrosis Germinal follicles Cystic follicles Atretic germinal follicles
18	Pos 6 M U	Streak	Normal stroma No follicles
19	FSH 2 MIU/ml LH 1.5 MIU/ml	Streak	Fibrous tissue Mesonephric remnants
20	FSH 2.4 MIU/ml LH<1.5 MIU/ml	Streak	Normal stroma No follicles

I (cont)

o	Gonadotropins	Gross appearance	Ovarian biopsy
	FSH 35 MIU/ml LH 27 5 MIU/ml	Streak	Stromal fibrosis No follicles
	FSH 46 9 MIU/ml LH 16 5 MIU/ml	Streak	Stromal fibrosis No follicles
l infantilism			
	FSH Pos 24 M U LH 33 IU/24hrs	Streak	Fibrous tissue
	Pos 48 M U	Streak	Fibrous tissue
nital absence of uterus			
	FSH 8 MIU/ml LH 15 MIU	Normal	Germinal follicles Graafian follicles
	FSH 3 MIU/ml LH 8 MIU/ml	Pos normal	Germinal folli les Graafian follicles
	FSH ? 5 MIU/ml LH 3 MIU/ml	Normal	Germinal follicles
	FSH 1? MIU/ml LH 18 MIU/ml	Normal	Corpus luteum
	FSH 7 5 MIU/ml LH 9 MIU/ml	Normal	Germinal follicles Graafian follicles
	FSH 4 2 MIU/ml LH 6 MIU/ml	Normal	Corpus luteum
	FSH 1 5 MIU/ml LH 6 15 MIU/ml	Normal	Germinal follicles Graafian follicles
	FSH 9 7 MIU/ml LH 10 8 MIU/ml	Normal	Germinal follicles Graafian follicles
	FSH 3 6 MIU/ml	Normal	Germinal follicles
	FSH 3 75 MIU/ml LH 7 0 MIU/ml	Normal	Germinal follicles Graafian follicles
	FSH 8 0 MIU/ml LH 10 0 MIU/ml	Cystic	Cystic follicles Germinal follicles Graafian follicles Luteinized stroma

d to thyroid and adrenal functions were done when ated

cal smears stained with toluidine blue were ex d for the percentage of Barr bodies according to the ique of Moore and Barr The karyotypes were de ned on peripheral blood lymphocytes by the Moor method (8)

ulation was documented with basal body tempera t arts and endometrial biopsies

ldoscopy was performed on 45 patients under ral analgesia using the following technique After sac puncture the culdoscope is inserted and pelvic nts visualized Then the cul-de sac perforation is ged with uterine dressing forceps and a Gutierrez p is introduced Under culdoscopic visualization the y is caught with the clamp at its inferior edge The oscope is then removed and the ovary is pulled gently e cul-de sa A suture is taken through the superior for stabilization By means of a sharp knife a biopsy is removed under direct vision and the site of biopsy is closed with interrupted chromic sutures When hemostasis is secured the ovary is replaced in its position The perforation in the cul-de sac is closed with a figure of eight suture after deflating air from the peritoneal cavity The patients are then taken to a recovery room and discharged home on the same day on mild analgesics

Laparoscopy was performed on 33 patients under general anesthesia using the following technique After securing a safe pneumoperitoneum with two liters of CO_2 a trocar is inserted infraumbilically an operative laparoscope introduced and pelvic organs visualized A second hole is made in the right lower abdomen and an ovarian biopsy forceps is inserted Using the cautery forceps to stabilize the ovary a punch biopsy is taken The biopsy site is cauterized to secure hemostasis in case of bleeding The infraumbilical incision is closed with a 4 zero chromic catgut subcuticular suture and the second hole with a simple skin chromic suture

Table II *Ovarian biopsies in 78 amenorrheic women*

Primary amenorrhea			35
With follicles			28
Normal follicles		24	
Normal stroma	23		
Luteinized stroma	1		
Fibrosed stroma	–		
Cystic follicles		4	
Normal stroma	1		
Luteinized stroma	2		
Fibrosed stroma	1		
With no follicles			7
Normal stroma	2		
Luteinized stroma	–		
Fibrosed stroma	5		
Secondary amenorrhea			43
With follicles			21
Normal follicles		16	
Normal stroma	15		
Luteinized stroma	1		
Fibrosed stroma	–		
Cystic follicles		5	
Normal stroma		3	
Luteinized stroma	2		
Fibrosed stroma	–		
With no follicles			22
Normal stroma	10		
Luteinized stroma	–		
Fibrosed stroma	12		

Table III *Distribution of 78 women with primary and secondary amenorrhea according to [illegible] apparatus and gonadotropin profile*

Primary amenorrhea			[illegible]
With follicles			[illegible]
Normal follicles		[illegible]	
Hypergonadotropic	[illegible]		
Hypogonadotropic	9		
Normotropic	10		
Cystic follicles		4	
Hypergonadotropic	[illegible]		
Hypogonadotropic	[illegible]		
Normotropic	1		
With no follicles			[illegible]
Hypergonadotropic	4		
Hypogonadotropic	3		
Secondary amenorrhea			[illegible]
With follicles			[illegible]
Normal follicles		16	
Hypergonadotropic	7		
Hypogonadotropic	9		
Cystic follicles		5	
Hypergonadotropic	1		
Hypogonadotropic	4		
With no follicles			[illegible]
Hypergonadotropic	[illegible]		
Hypogonadotropic	1		

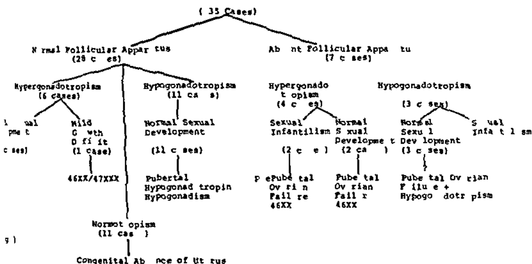
The biopsies obtained were sent to pathology where serial sections were made and stained with hematoxylin and eosin Their sizes were thought to be adequate enough to represent the ovary as a whole measuring 1×0 5 cm on the average They were assessed with particular reference to the germ cell and stromal compartments The presence of germinal follicles graafian follicles [illegible] corpora lutea and albicantia was carefully [illegible]

RESULTS

Primary amenorrhea Table I presents the [illegible] nadotropin values and ovarian histology [illegible]



Fig 1 Scanty germinal [illegible] 18 year-old woman with primary amenorrhea normal sexual development and elevated [illegible] pins (urinary gonadotropins [illegible] 48 mouse units) (Original [illegible] tion H & E ×10)



Classification of 35 cases of primary amenorrhea on ovarian biopsy

ones of women with primary amenorrhea 22 normal sexual development without prior gen administration 2 with sexual infantilism out hermaphroditism and 11 with congenital nce of the uterus

ble II presents the distribution of 35 wom with primary amenorrhea according to the logic description of ovarian follicles and ma from endoscopic ovarian biopsies There 8 biopsies with follicles which were normal ordial in 24 and cystic in 4 Those with normal les had a normal stroma except in 1 case where it was luteinized Those with cystic follicles had the stroma luteinized in 2 cases and fibrosed in 1

Table III shows the distribution of these cases according to their gonadotropin profile 6 were hypergonadotropic in spite of the presence of follicles (Fig 1) 11 were normotropic with cystic follicles luteinized stroma in 1 All of them had normal sexual development without prior estrogen stimulation (Fig 2) 11 cases with normotropism had congenital absence of the uterus and part or all of the vagina 1 of them had excessive hirsutism and all had normal sex chromosome patterns 6 cases with



Fig 3 Normal ovarian stroma without follicles in an 18 year-old girl with primary amenorrhea low serum gonadotropins (FSH 2 MIU/ml LH<1 5 MIU/ml) and well developed secondary sexual characteristics without prior estrogen stimulation (Original magnification H & E ×25)

Table IV *Gonadotropins and ovarian histology in 43 women with secondary amenorrhea*

Pat no	Gonadotropins	Gross appearance	Ovarian biopsy
With hypergonadotropism			
1	Pos 96 M U LH 1 500 IU/24hrs	Small	Normal stroma Germinal follicles
2	Pos 96 M U	Streak	Normal stroma Germinal follicles Corpus albicans
3	Pos 96 M U	Small	Luteinized stroma Germinal follicles
4	Pos 48 M U	Streak	Normal stroma Few atretic follicles
5	Pos 48 M U	Small	Normal stroma Few atretic follicles and Corpora albicantia
6	Neg 6 M U	Small	Normal stroma No follicles
7	Pos 96 M U LH 68 IU/24hrs	Small	Normal stroma No follicles
8	Pos 96 M U	Small	*Stromal fibrosis* No follicles
9	Pos 48 M U	Small	Normal stroma Few atretic follicles
10	Pos 48 M U LH 35 IU/24hrs	Small	Normal stroma Scanty germinal follicles Early corpus luteum
11	Pos 12 M U	Small	Normal stroma No follicles
12	Pos 12 M U LH>90 IU/24hrs	Small	Normal stroma Germinal follicles
13	FSH>50 M I U /ml LH 36 M I U /ml	Cystic Enlarged Thick Capsule	Stromal thecometosis Germinal follicles Few cystic follicles
14	FSH 46 MIU/ml LH 25 MIU/ml	Small	Stromal fibrosis No follicles
5	FSH>50 MIU LH 25 MIU/ml	Streak	Stromal fibrosis No follicles
16	FSH>50 MIU/ml LH>50 MIU/ml	Streak	Normal stroma No follicles
17	FSH>50 MIU/ml LH 34 MIU/ml	Small	Stromal fibrosis No follicles
18	FSH>50 MIU/ml LH 15 MIU/ml	Streak	Inactive stroma No follicles
19	FSH>50 MIU/ml LH 22 MIU/ml	Streak	Normal stroma No follicles
0	FSH>50 MIU/ml LH 33 MIU/ml	Small	Normal stroma No follicles
21	FSH>50 MIU/ml LH 24 7 MIU/ml	Streak	Stromal fibrosis No follicles
22	FSH 50 MIU/ml LH _6 MIU/ml	Small Small	Stromal fibrosis
23	FSH>50 MIU/ml LH 35 MIU/ml	Small	Normal stroma Germinal follicles

II (cont.)

no	Gonadotropins	Gross appearance	Ovarian biopsy
	FSH>50 MIU/ml LH 22 MIU/ml	Small	Stromal fibrosis No follicles
	FSH>100 MIU/ml LH 31 MIU/ml	Streak	Stromal fibrosis No follicles
	FSH> 50 MIU/ml LH 6 5 MIU/ml	Streak	Normal stroma Focal stromal hyper plasia No follicles
	FSH> 50 MIU/ml LH 50 MIU/ml	Small	Normal stroma Corpora albicantia
	FSH> 50 MIU/ml LH 21 MIU/ml	Streak	Stromal fibrosis No follicles
	FSH> 50 MIU/ml LH> 50 MIU/ml	Streak	Stromal fibrosis No follicles
hypogonadotropism			
	Neg 6 M U	Cystic	Thick capsule Normal stroma Cystic follicles
	Neg 6 M U	Cystic	Dermoid cyst Thick capsule Normal stroma Cystic follicles
	FSH Neg 6 M U LH 6 75 IU/24 hrs	Cystic	Thick capsule Luteinized stroma Cystic follicles
	FSH 13 MIU/ml LH 11 5 MIU/ml	Cystic	Thick capsule Luteinized stroma Cystic follicles
	FSH Pos 6 M U LH 24 IU/24 hrs	Normal	Normal stroma Germinal follicles
	FSH 2 5 MIU/ml LH 4 75 MIU/ml	Normal	Normal stroma Germinal follicles
	FSH 2 1 MIU/ml LH 2 2 MIU/ml	Normal	Normal stroma Germinal follicles
	FSH 4 2 MIU/ml LH<1 5 MIU/ml	Normal	Normal stroma Germinal follicles Atretic follicles
	FSH 4 2 MIU/ml LH 9 MIU/ml	Normal	Normal stroma Germinal follicles
	Neg 6 M U	Normal	Normal stroma Germinal follicles Atrophic follicles
	Neg 6 M U	Normal	Normal stroma Germinal follicles Graafian follicles
	FSH 1 5 MIU/ml LH 9 MIU/ml	Normal	Normal stroma Germinal follicles Graafian follicles
	Neg 6 M U	Small	Normal stroma No follicles



Fig 4 Scanty germinal stromal thecoma ... old woman para 3 with amenorrhea of 1 year ... high serum gonadotropins ... MIU/ml LH 36 MIU/ml ... magnification H & E×10)

hypergonadotropism had normal sexual development with 46XX sex chromosome patterns except in 1 case who had a mild growth deficit (155 cm 55 kg) and a mosaic sex chromosome pattern with a karyotype on peripheral lymphocytes showing 2% with 47XXX and the rest 46XX 11 cases with hypogonadotropism had normal sexual development and 46XX on the karyotypes

There were 7 biopsies of streak gonads without ovarian follicles 4 were hypergonadotropic with stromal fibrosis and 46XX sex chromatin patterns Of these 2 had sexual infantilism without hermaphroditism and 2 had their secondary sex characteristics developed without prior estrogen administration (Fig 2) 3 were hypogonadotropic ... 46XX sex chromosome complement ... veloped secondary sex characteristics (Fig ... ovarian stroma normal in 2 (Fig 3) fibrosed in 1

Secondary amenorrhea Table IV presents ... gonadotropin values and ovarian histology ... catagories of women with secondary amenorrhea ... 29 with elevated gonadotropins and 14 ... gonadotropin levels

Table II presents the distribution of ... with secondary amenorrhea according ... histologic description of ovarian ... stroma from endoscopic ovarian biopsies There were 21 biopsies with follicles which were ...



Fig 5 Scanty germinal ... an early corpus ... year-old woman with secondary amenorrhea of 3 years ... secondary infertility of 4 years ... tion and high gonadotropins ... 46 MIU/ml LH ... MIU ... nal magnification H & E ...



Fig 6 Hyperplasia of theca interna and stromal luteinization in a 24-year-old woman with secondary amenorrhea of 4 years duration who failed to ovulate on clomid (Original magnification H & E ×10)

nd cystic in 5 Those with normal follicles had nal stroma except in 1 case where it was nized Those with cystic follicles had a normal na in 3 cases and a luteinized one in 2

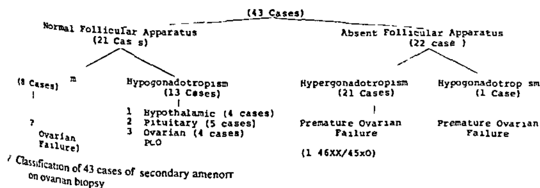
ble III shows their distribution according to gonadotropin profile 8 cases were hyper dotropic in spite of the presence of follicles stromal comatosis in 1 (Fig 4) and an early us luteum in another (Fig 5) 13 cases were gonadotropic with cystic follicles in 4 who also stromal luteinization (Fig 6)

ere were 22 biopsies without ovarian follicles a normal stroma in 10 and a fibrosed stroma in f them (Table II) All except 1 were hyper dotropic (Table III)

the light of endoscopic and histologic findings is possible to distribute patients with primary amenorrhea into 2 main groups in relation to subsequent management (Fig 2) There were 17 cases with ovarian follicles and no mullerian duct abnormalities Human menopausal gonadotropins were administered to 5 of them who had high endogenous gonadotropin levels and was successful in 1 evidenced by a biphasic temperature chart while it failed in 4 even on high dose schedules

HMG was also administered to 7 of them who had low gonadotropins and was successful in 2 only It failed in 2 cases who had cystic follicles even with very high dose schedules In 1 of the patients a Y chromosome was present She refused surgery for removal of the gonads Estrogens were administered to those with sexual infantilism to aid secondary sexual development

Patients with secondary amenorrhea were also



Classification of 43 cases of secondary amenorr on ovarian biopsy

distributed into 2 groups (Fig 7) 21 cases had ovarian follicles Human menopausal gonadotropins were administered to 4 of them who had high endogenous gonadotropins but failed to induce ovulation in any including 1 case who had an early corpus luteum on a biopsy done just prior to the initiation of therapy

13 cases with hypogonadotropism were all refractory to clomid and gonadotropin therapy 9 had a central pathology 1 of them got pregnant on ergocryptin and 1 had a pituitary adenoma that was revealed by radiology a year following the biopsy It was removed transphenoidally 4 had polycystic ovaries 1 of whom got pregnant after wedge resection

The 78 ovarian biopsies performed were all uneventful without complications except in 1 case which following the biopsy by culdoscopy had bleeding from the ovarian site that could not be controlled through the vaginal incision A laparatomy was performed and on the 5th hospital day she was discharged in good condition

DISCUSSION

The fertility prognosis of many amenorrheic women has changed considerably since agents for the induction of ovulation have become available However the therapy is expensive and entails some undesirable side effects Hence accurate assessment of ovarian histology can be helpful in the selection of patients and in anticipating their therapeutic responses Patients with primary amenorrhea who have normal sexual development without prior estrogen stimulation and with no mullerian duct abnormalities could either have high or low endogenous gonadotropins Out of 14 such cases with hypogonadotropism ovarian biopsies revealed the absence of follicles in 3 Gonadotropins could have been given to these patients to no avail The only way we could explain their amenorrhea was by assuming a central as well as an ovarian pathology manifested through hypogonadotropism plus pubertal ovarian failure 8 other cases with hypergonadotropism revealed the absence of follicles in 2 and their presence in 6 Those who had no follicles should have been producing enough estrogens at one time to account for their normal secondary sexual characteristics The follicles they could have had should have undergone atresia and disappeared before the biopsies were performed

Their amenorrhea would be due to a [illegible] ovarian failure in contrast to the [illegible] is characterized by sexual infa[illegible] follicles had a similar ovarian histolog[illegible] to the cases reported by Jones (4) a[illegible] They all had numerous primordial f[illegible] graafian follicles in 2 and an old corpus l[illegible] There was evidence also of increased LH [illegible] tion in 1 case who had stromal lu[illegible] cystic follicles Their ovaries however [illegible] seem to be completely resistant to g[illegible] stimulation endogenous or exogenous [illegible] by an old corpus luteum in 1 and the p[illegible] sponse of another case to HMG ther[illegible] reason for a decreased sensitivity of these f[illegible] and an altered feedback effect they [illegible] gonadotropin production remains to be [illegible]

Patients whose ovaries fail prematurely can[illegible] distinguished clinically from those with othe[illegible] of secondary amenorrhea Although the d[illegible] almost certain if the excretion of gonad[illegible] increased Yet ovarian biopsies perf[illegible] such cases revealed the presence of ovarian [illegible] in 8 of them with an early corpus luteum in 1 cystic follicles in another case [illegible] of them sh[illegible] evidence of increased LH stimula[illegible] stromal luteinization (9 16) The infert[illegible] of these patients and their refractoriness to e[illegible] nous gonadotropins speak for an altered f[illegible] function An ovarian biopsy however w[illegible] the physician to give an accurate prognosis [illegible] a serious diagnosis Whether an [illegible] biopsy ought to be considered in patien[illegible] ondary amenorrhea who have low end[illegible] gonadotropins and who are refractory to [illegible] stimulation depends on the availability of L[illegible] ory methods to delineate those with hyp[illegible] etiology from those with pituitary or ova[illegible] hology We believe however that certa[illegible] polycystic ovary syndrome who show [illegible] thecomatosis on histology may benefit [illegible] ovarian wedge resection

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Submitted for publication Feb 6 1978

Karam Karam
Department of Obstetrics and Gynecology
American University Hospital
Beirut
Lebanon

Acta Obstet Gynecol Scand 57 313-316 1978

CAP HCS AND URINARY OESTRIOL ASSAYS IN DIABETIC PREGNANCY

Gunnar Rydén and Goran Berg

From the Department of Obstetrics and Gynecology University Hospital Linkoping Sweden

act The value of serial estimations of plasma CAP and urinary oestriol assays in pregnancies compli with diabetes has been studied The material con of 31 patients 16 of whom delivered normal infants 15 delivered newborns with diabetic foetopathy It is luded that the levels of CAP HCS and urinary nol excretion in diabetic pregnancies are comparable se found in normal pregnancy No significant differ s in the biochemical parameters were detected be n diabetic women who delivered infants with pathy compared to diabetic women who delivered al infants The maternal oestriol excretion was how somewhat higher in diabetic women who delivered s with macrosomia

cent study (14) dealt with the value of serial minations of cystine aminopeptidase (CAP) human chorionic somato mammotrophin (HCS) ternal plasma and maternal urinary oestriol ys in risk pregnancies such as preeclampsia rtension and intrauterine growth retardation as concluded that all three tests can yield infor on about the condition of the fetus and/or nta and that more accurate information con ing the fetoplacental unit can be gained by ining oestriol assays with CAP or HCS assays abetic pregnancies are accompanied by a high lence of complications in the newborn Numer s udies have demonstrated the clinical value of urinary oestriol determinations in diabetic ancies (see Persson et al (12) The value of estimations is less clear Some authors (16 18) reported high HCS values in diabetic preg s whereas others (3 9 13) have found nor values The diabetogenic properties of HCS the levels of this hormone of special interest egnancies complicated by diabetes Reports on estimations in diabetic pregnancies are few

Kleiner et al (7) concluded that CAP assays should be used in association with oestriol assays when assessing risk pregnancies such as diabetes Chapman et al (1) found higher CAP values in diabetic pregnancies compared to normal preg nancies whereas no such difference was observed for urinary oestriol assays

The purpose of the present investigation was to study the plasma CAP HCS and urinary oestriol levels in diabetic pregnancy with special reference to the ability to predict diabetic foetopathy

MATERIAL

The material consisted of 31 patients with insulin requiring diabetes They were followed by serial assays of CAP HCS and urinary oestriol from the 32nd week of pregnancy until delivery Plasma CAP and HCS assays were performed at least once a week Urinary oestriol assays were performed daily or every other day but only assays performed on the same day as the CAP and HCS assays are included in this study

The patients were divided into two groups one of 16 patients who delivered normal infants (within ±2 S D for the gestational age) and a second of 15 patients who deliv ered infants with signs of foetopathy The diagnosis was confirmed by a pediatrician according to the usual clinical criteria Patients with toxaemia intrauterine growth re tardation and hypertension were excluded from the pres ent study as these conditions per se can influence the biochemical values

The diabetic women were managed according to the principles described by Molsted (10) The patients were admitted to the hospital at the beginning of the pregnancy for regulation of the blood glucose with an outpatient follow up every second week A second hospital stay was arranged in the [illegible] week of pregnancy From the [illegible] week of pregnancy until delivery the patients had blood glucose estimations at least five times daily (l cur 2 11 19 and 23) and urinary glucose was measured in [illegible] hour specimens

Table I *Weekly maternal blood glucose levels (mean ± S D)*

Pregnancy week	Normal infant group		Diabetic foetopathy group	
	n	mmol/l	*n*	mmol/l
32	9	5 9±1 17	8	6 7±1 68
33	10	5 6±1 00	11	6 2±1 27
34	14	5 6±1 08	12	6 1±1 64
35	14	5 6±1 40	13	6 2±2 02
36	15	5 4±0 96	13	5 4±1 13
37	15	5 2±1 13	15	6 0±1 69
38	14	4 7±0 75	14	5 2±5 15
39	11	4 7±0 95	7	5 1±0 95

Table II *Mean value of the [illegible] standard deviation of the blood [illegible] (mean ± S D)*

Pregnancy week	Normal infant group		Diabetic foetopathy group	
	n	mmol/l	*n*	mmol/l
32	9	2 5±0 55	8	[illegible]
33	10	2 6±0 75	11	[illegible]
34	14	2.5±0 63	1[illegible]	[illegible]
35	14	[illegible]3±0 93	13	[illegible]
36	15	[illegible]3±0 66	13	[illegible]
37	15	[illegible]3±0 80	15	[illegible]
38	14	1 9±0 69	14	[illegible]
39	11	2 1±0 83	7	[illegible]

METHODS

Urinary oestriol assays were made according to Hainsworth & Hall (4) Plasma cystine aminopeptidase was determined according to Peeters (11) later modified according to Tovey (20) A comparative study of the two methods performed on 106 samples gave a correlation coefficient of 0 96 The calculation of CAP activity was performed according to Tovey (20) Plasma human chorionic somato-mammotrophin was measured according to Letchworth et al (8)

RESULTS

An analysis of the maternal blood glucose levels from the 32nd week of pregnancy until delivery is reported in Table I The mean maternal blood glucose level for each week calculated from the five daily blood glucose estimations performed demonstrates the generally higher levels among patients who delivered infants with diabetic foetopathy The weekly individual standard deviation has also been compared to see if diabetic women with foetopathic newborns have greater fluctuations in blood glucose levels As shown in Table II no significant difference was found between [illegible] groups

The mean birth weight of the infants [illegible] tional age Apgar score after 1 and 5 min [illegible] lowest blood sugar in the neonatal period [illegible] sented in Table III There was no perinatal [illegible] The increased incidence of hypoglycaemia observed in diabetic foetopathy (5) could [illegible] demonstrated in the present study This [illegible] explained by the management of the newborn [illegible] early feeding

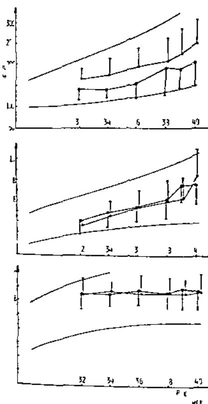
The results of the biochemical te[illegible] in Fig 1 For comparison the figure [illegible] 5th and 95th percentile levels in normal preg[illegible] quoted from Rydén & Kågedal (14) The [illegible] obtained in diabetic pregnancy are compa[illegible] normal pregnancy Concerning CAP and [illegible] difference was observed between the two [illegible] diabetic women examined Women who [illegible] infants with diabetic foetopathy had [illegible] higher oestriol values than the normal gr[illegible]

A regression analysis was performed [illegible] relationship between the biochemical tes[illegible]

Table III *Birth weight gestational age Apgar score after 1 and 5 min and lowest blood [illegible] newborns*

Mean value ± S D

	n	Gestational age (weeks)	Birth weight (g)	Apgar score		Lowest [illegible] (mmol/l)
				1 min	5 min	
Normal infants	16	39 3±1 39	3 [illegible]31±4[illegible]4	8 6±0 70	9 1±0 [illegible]4	1 8±0 6[illegible]
Diabetic foetopathy	15	38 9±1 19	3 9[illegible]9±47[illegible]	8 0±[illegible]23	9 4 0 61	1 9±0 [illegible]



Mean plasma CAP HCS and urinary oestriol val (+S D) in diabetic women who delivered normal ts (x—x) and infants with diabetic foetopathy The 5th and 95 percentile levels in normal preg y are also given

nt birth weight and placental weight respective The last value before delivery was compared the weight of the placenta and the infant birth ht In patients who delivered normal infants a elation was found between urinary oestriol ex on and infant birth weight ($r=0\ 49$ $P=0\ 02$) ever urinary oestriol excretion correlated bet placental weight ($r=0\ 69$ $P=0\ 002$) CAP correlated to placental weight ($r=0\ 52$ 01) but not to infant birth weight whereas no tion was found between HCS and either al or birth weight In pregnancies complicat diabetic foetopathy no correlation was between either placental or infant weight he biochemical tests studied

DISCUSSION AND CONCLUSION

ary oestriol assays are generally accepted valuable method for assessing the condition of the foetoplacental unit in diabetic pregnancy (13) The value of placental function tests such as CAP and HCS is less clear Chapman et al (1) observed higher CAP values from 30 weeks onwards in diabetic pregnancy compared to normal pregnancy and suggest that CAP assays might be a valuable parameter in evaluating the condition of the foetus in poorly controlled diabetic pregnancies This could not be confirmed in the present study The CAP values in the patients who delivered babies with diabetic foetopathy did not differ from those in patients who delivered normal infants Both high (15 16 18) and normal HCS values (9 13) have previously been reported in diabetic pregnancies Other authors (2 19 21) have found high HCS values in pregnant patients with poorly controlled diabetes and normal values in well-controlled diabetes The diabetogenic property of HCS is well established (6) High and increasing HCS values could possibly influence the maternal glucose metabolism and give rise to a more intractable blood glucose level and hence a greater risk of diabetic foetopathy Tyson & Hock (20) have proposed that the HCS levels per se can be responsible for the imbalance of blood glucose homeostasis that is often seen in diabetic pregnancy The present results as well as the finding of Spellacy & Cohn (16) that the rising insulin requirements in diabetic pregnancy are not related to the increasing production of HCS do not support the theory proposed by Tyson & Hock

The following conclusions can be drawn Neither CAP nor HCS are of value in predicting the condition of the foetus at birth with respect to diabetic foetopathy The levels of CAP and HCS in diabetic pregnancy are comparable to those found in normal pregnancy

Perinatal loss in late diabetic pregnancy is seldom dependent on the placenta the usual cause being a derangement of the glucose homeostasis which exerts its effect directly on the foetus The production of oestriol during pregnancy is primarily dependent on foetal adrenal function so that changes in the condition of the foetus are reflected in the maternal oestriol excretion hence the clinical value of serial oestriol assays in diabetic pregnancy However if the diabetic pregnancy is complicated by toxaemia or intrauterine growth retardation both HCS assays (13) and CAP assays (7 14) can be useful tools besides oestriol assays for monitoring the foetus

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Submitted for publication May 5 1977

Gunnar Ryden
Dept of Obstetrics and Gynecology
University Hospital
S 581 85 Linkoping Sweden

Acta Obstet Gynecol Scand 57 317–322 1978

THE EFFECTS OF ISOPROTERENOL ON FETAL OXYGENATION

R E Myers I Joelsson and K Adamsons

From the Laboratory of Perinatal Physiology
National Institute of Neurological and Communicative
Disorders and Stroke National Institutes of Health Bethesda Maryland USA
the Department of Obstetrics and Gynecology Umeå University Umeå Sweden
and the Department of Obstetrics and Gynecology Brown University
Providence Rhode Island USA

act Infusion of isoproterenol (1 μg/kg/min i v) into anesthetized pregnant rhesus monkey near term con ntly reduced fetal oxygenation despite diminishing metrial activity The decline in pO of fetal arterial d (mean=4 3±? 3 mmHg S D) was accompanied by crease in pCO tension (mean=4 6±? 7 mmHg) and a ne in pH (mean=0 04±0 02 S D) There was an in e in heart rate and a widening of pulse pressure in the er and also in the adequately oxygenated fetus pro g evidence that the agent crosses the placenta The ly oxygenated fetuses developed bradycardia and tension Administration of isoproterenol directly to fetus elicited similar changes in the composition of d and in blood pressure and heart rate to those rved after administration of the agent to the mother

ariety of synthetic beta receptor stimulating nes have been used during the last five years to age patients in premature labor (1–4) and to t fetal asphyxia produced by excessive uterine vity (5) When these agents are administered to ratory primates they have been found to re the frequency of uterine contractions both in ntaneous and in induced labor (6) These same ts also alter the conductance of blood vessels ughout the body and thus modify the distribu of blood flow Because the blood vessels of the us like those of other viscera are poorly sup d with beta adrenergic receptors administration beta adrenergic agents could reduce uterine d flow and hence impair oxygenation of the s This would pertain particularly if the agent uces mean arterial blood pressure of the mother licits compensatory vasoconstriction in the vis al circulation

cause the infusion of epinephrine into the pre t primate is known to cause asphyxia of the s (7) it seemed of interest to determine the effects of a pure beta receptor stimulating agent

Currently available clinical literature does not provide information as to the effects of beta adrenergic receptor stimulating agents on the oxy genation of the fetus When these agents are used in the treatment of premature labor the fetus is not usually accessible for blood sampling However there is a study in which a slight reduction in fetal pH was observed when ritodrine was infused into the mother for longer than 30 minutes (8) When beta adrenergic stimulating agents are used to suppress excessive uterine activity the effects of this reduction in uterine activity on the oxygenation of the fetus cannot be separated from those brought about by the action of these drugs on the con ductance of the blood vessels supplying the uterus and other organs Beta mimetic drugs administered to the mother could affect the oxygenation of the fetus by altering the blood flow through the umbili cal vessels after their transfer to the fetus

The present study was conducted under condi tions of low initial uterine activity in order to focus specifically on those alterations in fetal oxygenation that result from changes in the circulatory state of the mother and fetus

MATERIAL AND METHODS

Fifteen rhesus monkeys in the last decile of pregnancy were used Isoproterenol was administered to the mother by constant i v infusion on 13 occasions in 11 animals to the fetus on 9 occations in 7 animals and finally to the mother by rapid i v injection 6 times in 4 animals In every instance a rest period lasting from 55 to 90 min was al lowed between infusions or injections to the same animal to permit a full recovery of the function of the car diovascular system and of the composition of the blood

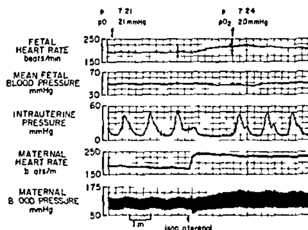


Fig 1 Fetal and maternal heart rates and blood pressures and intrauterine pressure before and after rapid injection of isoproterenol (8 μg/kg i v) to the anesthetized pregnant rhesus monkey near term Note the increase in heart rate and the slight fall in blood pressure in the presence of an essentially constant state of oxygenation

back to baseline values The duration of pregnancy was known for each animal with an accuracy of ±2 days The animals body weights varied from 6 2 to 9 4 kg

Hysterotomy was performed under pentobarbital anesthesia (35 mg/kg i v) Polyethylene catheters were inserted into the femoral artery and vein of the mother and of the fetus to record blood pressure and heart rate and to withdraw blood samples as well as to administer isoproterenol The intrauterine pressure was recorded by a catheter placed into the amniotic cavity All samples of maternal and fetal arterial blood were analyzed for pH pO_2 and pCO_2 using appropriate microelectrodes (London Company) Throughout the experiment the oxygen tension of maternal arterial blood was maintained in the range of 90 to 120 mmHg by adjustments of the oxygen concentration of the inspired gas mixture The mother s eep colonic temperature was controlled in the range of 7 to 38 C using a servo modulated overhead heat shield

During the control period each mother was given 250 ml of 5% dextrose in water by i v drip The blood volume of the fetus was maintained throughout the study period by replacing the blood withdrawn with an equivalent volume of maternal blood A more detailed account of all proce dures used has been given earlier (7)

The isoproterenol solutions were prepared fresh to con tain 10 μg/ml of the base in isotonic saline The drug was administered through the femoral vein catheter of the mother or fetus either by rapid injection or by infusion at a constant rate over a 20-min period In a single instance the infusion was discontinued before ?0 min elapsed because of the threat of imminent death of the fetus due to severe asphyxia The dosage for isoproterenol infusion to the mother was 1μg/kg/min and to the fetus 0 5 to 2 0 μg/kg/min The dosage for rapid injection into the mother ranged from 2 to 8 μg/kg In calculating the dose for infusion directly into the fetus the combined weights of the fetus and placenta were assumed to be 500 gm

RESULTS

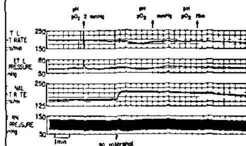
Control values of the mothers and fetuses prior to administration of isoproterenol

The maternal heart rates under anesthesia ranged from 125 to 175 beats/min while their blood pressures ranged from 120/75 to 170/110 mmHg The maternal pH pO_2 and pCO_2 values while they were breathing spontaneously ranged from 7 3? to 7 4? 84 to 108 mmHg and 28 to 38 mmHg respectively Uterine activity was slight to moderate in all instances The so-called resting tone ranged from ? to 8 mmHg the intervals between contractions ranged from 3 to 12 min and the amplitudes of the contractions ranged between 2 and 30 mmHg In most instances the amplitudes of contractions remained less than 10 mmHg

The fetal heart rates ranged between 175 and 2?? beats/min while the blood pressures ranged from 53/33 to 70/40 The pH values of blood obtained from the fetal lower thoracic aorta averaged 7.2? with a range of 7 20 to 7 3? The mean pO was ? with a range of 19 to 33 mmHg and that of pCO_2 was 45 with a range of 38 to 47 mmHg The mean values of red cell concentrations of maternal and fetal arterial bloods were 35% and 45% with ranges of 31 to 37% and 42 to 46% respectively

Maternal and fetal responses to rapid injection of isoproterenol to the mother

Isoproterenol was administered directly to the mother by rapid injection in a dose which ranged from 2 to 8 μg/kg in 6 instances in 4 animals These injections in this dose range produced a rapid increase in maternal heart rat which ranged from 1? to 60% (see Figs 1 2 and 3) In 5 of the 6 instances, the systolic pressure rose from 9 to 36% while the diastolic pressure changed variably from −1? to +10% In the remaining animal the injection caused an initial decrease of 7% in both the systolic and distolic blood pressure In those instances where regular intermittent contractions of the uterus were present the injection of isoproterenol increased the interval between contractions but had no effect on the amplitude The effects on heart rate blood pressure and uterine activity were transient and preinjection values were restored within 15 min Maximal changes in heart rate and blood pressure were attained already at a dose of 2μg/kg



? Fetal and maternal heart rates and blood pressures ng injection of isoproterenol (2 μg/kg) into the pre t rhesus monkey near term Note transient decrease al heart rate and blood pressure and in pH and pO_2 al arterial blood

he rapid injection of isoproterenol into the her caused an increase in fetal heart rate similar at documented in Fig 1 in 4 of 6 instances This ase in fetal heart rate lasted from 5 to 10 min could be detected within 40 seconds after the roterenol was administered to the mother The pCO_2 and pH values of fetal arterial blood n sampled at 5 10 and 20 min after injection ed no significant changes However in two ances the injection of isoproterenol to the her led to clearly defined episodes of dycardia and hypotension in the fetuses These meters recovered to their preinjection values re the 5 min blood samples were drawn When arterial blood of these two fetuses was sampled ng the period of maximal bradycardia signific decreases in pO_2 were observed e g the pO_2 eased from 21 to 17 in one and from 13 to 9 Hg in the other The arterial blood pO_2 s re ed to their preinjection values within 10 min in instances (See Figs 2 and 3)

and fetal response to infusion
into the mother

terenol was administered to the mother by infusion (l/μg/kg/min) on 13 occasions in 10 These infusions produced a prompt in in heart rate of the mother with a mean of 34% and a standard deviation of ±10% maternal systolic blood pressure increased antly by a mean value of 14±4% S D diastolic blood pressure decreased by a mean ue of 9±6% S D When definite uterine contrac were present the intercontraction interval was prolonged by up to two-fold At the same time the amplitudes of the uterine contractions were altered only slightly or not at all These effects on the myometrium were more marked at the begin ning than toward the end of the period of infusion The pO_2 of maternal arterial blood decreased in all instances This decrease ranged from 19 to 45 mmHg To compensate for this decrease the oxy gen concentration in the inspired gas mixture of the mother was increased until the maternal arterial blood samples showed a pO_2 that was restored to the preinfusion values in all instances The pCO_2 and pH values of maternal arterial blood did not change significantly The maternal cardiovascular changes were maximal during the early phases of infusion and the values generally recovered to preinjection levels within 10 min of termination of infusion

The infusion of isoproterenol to the mother caused no changes in blood pressure or heart rate of the adequately oxygenated fetus However it did lead to reductions in fetal aortic blood pO_2 in all instances This decrease ranged from 2 to 8 mmHg with a mean value of 4 3 and a standard deviation of ±2 3 mmHg This decrease in oxygen pressure of fetal blood was accompanied by a mean increase in pCO_2 of 4 6±2 7 mmHg S D and a mean decrease in pH of 0 04±0 02 S D The composition of fetal

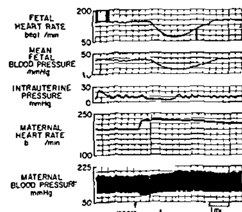


Fig 3 Fetal and maternal heart rates and blood pressures and intrauterine pressure after a rapid injection of isoproterenol (2 μg/kg i v) to anesthetized rhesus monkey near term with severaly acidotic and hypoxic fetus (pH=6 83 pO_2=13 mmHg) Note the induction of transient bradycadria and hypotension in the fetus despite a decrease in uterine activity The changes in vital signs were associated with a fall of pO_2 in fetal arterial blood from 13 to 9 mmHg

arterial blood recovered to its preinjection values in all instances within 20 min after drug infusion was terminated

Fetal response to infusion of isoproterenol to the fetus

Isoproterenol was infused intravenously directly to the fetus in 9 instances in 7 animals in the dose range of 0 5 to 2 0 μg/kg/min These infusions led to average increase in fetal heart rate of 15%±7% S D This was accompanied by small and variable changes in fetal systolic blood pressure (mean=2 6±5 5% S D) and consistent decreases in diastolic blood pressure which ranged from 13 to 32% (mean=16 7±6 1% S D) These alterations in fetal cardiovascular function were accompanied by decreases in fetal pO_2 (mean=5 9±2 9 mmHg S D) and pH (man=0 07±0 03 S D) and increases in pCO_2 (mean=7 6±5 1 mmHg S D) The heart rate and blood pressure changes elicited by isoproterenol infusion disappeared rapidly after infusion was discontinued whereas up to 20 min were required for the chemical composition of the blood to return to preinfusion values

DISCUSSION

Intravenous infusion of isoproterenol into pregnant rhesus monkeys consistently elicited a decrease in oxygen tension of the maternal arterial blood Review of the literature failed to uncover any information regarding such an effect on arterial pO_2 during pregnancy in any species The few clinical reports that cite any alterations in oxygenation during infusion or inhalation of beta adrenergic drugs describe small reductions in arterial blood pO_2 in asthmatic patients while failing to demonstrate such changes in controls (9 10) The authors of these studies attribute the reductions in arterial blood pO_2 in asthmatic patients to an increased maldistribution of pulmonary ventilation due to uneven penetrance of the aerosol within the tracheobronchial tree Because in the present study isoproterenol was administered intravenously and hence could not affect the terminal air ducts nonhomogeneously the significant decreases in arterial blood pO_2 observed are more likely due to an increased right to left shunting within the pulmonary vasculature This interpretation is consistent with the finding that infusion of isoproterenol increases the conductance of the pulmonary blood vessels and augments the blood volume of the capillary bed in isolated lung preparations (11)

The rapid injection of isoproterenol in the mothers consistently increased the heart rate and widened the pulse pressure of the well-oxygenated fetuses These changes in cardiovascular function of the fetuses followed similar changes observed in the mothers by an interval of about 40 sec and persisted for a similar period of time Increase in maternal heart rate accompanied by a similar increase in the fetus has also been observed regularly in man in conjunction with administration of beta adrenergic agents (8 11) Because the fetal pO_2 regularly decreased following administration of isoproterenol to the mother the increase in fetal heart rate and pulse pressure can be attributed only to an effect of isoproterenol acting directly on the fetus following its transfer from the mother

When isoproterenol was administered to the mothers of poorly oxygenated fetuses bradycardia and hypotension of the fetuses was observed The differences in cardiovascular response of the fetuses according to their preexisting pO_2 values are explained by the fact that a relatively large reduction in arterial blood pO_2 is required to el… fe… bradycardia and hypotension in the well-oxygenated fetus Lowering of pO_2 of such magnitude did not occur during the fusion o… isoproterenol to the mothers of well-oxygenated fetuses

Beta adrenergic receptor stimulating agents can reduce oxygenation of the fetus through sever… mechanisms The first is the reduction in mater… arterial pO_2 presumably due to increased in… trapulmonary right to left shunting The secu… consists of reduction of uterine or intervillous spa… blood flow by increasing the conductance of the blood vessels supplying organs which are rich w… beta adrenergic receptors Such changes are m… likely to occur with beta adrenergic agents that have little positive chronotropic and inotropic… cardiac ef… fect and hence do not increase appreciably cardiac output It should also be recognized that ma… nance of mean arterial blood pressure during administration of the agent does not ensure main… nance of a given flow rate to the uterus or the intervillous space This is due to the fact th… flexly mediated regional vasoconstriction with… resultant reduction in conductance is not linked… specific changes in mean arterial pressure

The third mechanism depends on a direct ef…

oproterenol on fetal vasculature diverting the t ventricular output of the fetus from the perfu of the placenta

he relative contribution made by these hanisms will depend on the status of uterine d flow the time of administration of the agent lation to uterine contractions the degree of trance of the drug into the fetal compartment eactivity and vascular status of other areas of maternal vascular tree and the bioavailability e compound

thou_h an extensive literature depicts the iovascular effects of infusion of isoproterenol other related compounds in a variety of species e nonpregnant state little information is avail regarding its effect on cardiac output and reg l blood flow distribution during pregnancy In pregnant ewe infusion of isoproterenol has reported to increase slightly uterine blood flow ite of a decrease in perfusion pressure (12) finding has been interpreted as indicating that uterine circulation is under the regulatory con of beta adrenergic receptors More recently rary results have been obtained in studies with r synthetic beta adrenergic receptor stimulating ts including isoxsuprine and ritodrine where ions into awake pregnant ewes have led to ter than 30% reductions in uterine blood flow The present data favor the contention that the onsiveness of uterine blood vessels including piral arteries to beta adrenergic stimulants is than that of blood vessels elsewhere in the body that their administration leads to a decrease r than an increase in perfusion of the intervill space

he hypoxic and acidotic fetus was particularly itive to changes in circulation in the mother t about by administration of isoproterenol It d be emphasized however that it is the low tolerance of the asphyxiated fetus to further s in oxygenation that accounts for this omenon rather than any specific sensitivity of animals to the pharmacologic agent

effects of isoproterenol upon pO_2 of fetal al blood as reported in the present study are ary to those inferred from clinical experience other beta mimetic agents used to control ex ive uterine activity Caldeyro-Barcia and co- 5) obtained evidence of an amelioration of l condition as judged by improvement of fetal rate patterns following administration of orciprenaline to the mother in hyperactive labor Saling and his collaborators have also provided data taken from a larger patient series that describe a definite value in administering beta mimetic agents for the treatment of fetal asphyxia under such circumstances (14)

Several factors may account for these apparent discrepancies in outcome In our studies isoproterenol was administered to pregnant monk eys exhibiting only slight uterine activity in con trast to the above described clinical studies where corresponding agents were employed only in the presence of a uterine activity so great as to cause a clinically significant asphyxia of the fetus Reduc tion of uterine activity under such conditions is likely to lead to a net increase in intervillous space blood flow in spite of the increase in vascular con ductance of blood vessels of other organs Other factors that may contribute to differences in out come include differences in sedation or anesthe sia of the mother and fetus differences in phar macologic properties of the various betamimetic drugs used and differences in reactivity of the uterus and cardiovascular system among differ ent species of primates

Isoproterenol administered directly to the fetus causes significant reductions in oxygen pressure of fetal aortic blood without inducing any changes in heart rate or blood pressure of the mother This direct drug effect on the fetus likely results from an increased conductance of the blood vessels supply ing the lungs and other tissues of the fetus diverting blood flow from the umbilical circulation This in terpretation is favored by the fact that infusion of isoproterenol directly into the sheep fetus markedly increases blood flow through the lungs (15)

ACKNOWLEDGMENTS

The authors express their appreciation to Mr Esteban Monell Torrens for his assistance in carrying out this study

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Submitted for publication Febr 15 1977

Ingemar Joelsson M D
Department of Obstetrics and Gynecology
Umeå University Hospital
S 901 85 Umeå
Sweden

Acta Obstet Gynecol Scand 57 323–326 1978

EFFECTS OF TERBUTALINE ON THE PRESSURE VOLUME RELATIONSHIP IN FETAL RABBIT LUNG

B Bergman T Hedner and P Lundborg

From the Department of Obstetrics and Gynaecology Centrallasarettet Molndal and the Department of Pharmacology University of Goteborg Goteborg Sweden

ract The pressure volume relationship in preterm t lung was studied at 28 days of gestation Injection of mg terbutaline a selective β_2-receptor stimulating significantly increased the volume of air at equiva low transpulmonary pressures compared to a e treated group and an untreated group These find indicate an increased pulmonary distensibility of the rabbit lung after terbutaline administration The hanism of action is discussed and surfactant mediated ts are suggested to be the probable explanation

pathic respiratory distress syndrome (IRDS) hyaline membrane disease (HMD) is a common serious condition occurring mainly in preterm nts Clinical studies during recent years have an that the risk of HMD can be reduced by inistration of various drugs to the mother dur pregnancy

he possibility that corticosteroids present in fetal circulation may influence pulmonary mat n was reported by Buckingham (3) Liggins and Liggins & Howie (13) Other investigators nd a similar effect by isoxsuprine (8 17) drine (?) heroine (6) and by thyroxine (14 16) clinical study we have adminstered terbutaline elective β_2-receptor stimulating drug during in an attempt to arrest premature labour where delivery occurred in spite of this tment we found a remarkably low incidence of) as compared to a control group which had ved no such treatment (1)

aim of the present investigation was to ex the potential usefulness of terbutaline in this by studying its effect on the fetal rabbit lung rdized experimental conditions

MATERIAL AND METHODS

e and black rabbits of Danish rural breed were one or two bucks under direct observation Copulation was considered as zero time of gestation The does were kept in separate cages in the department and fed on standard pellets and water ad libitum

Three days before term at 28 days of gestation the pregnant does were anesthetized with ether administered by open mask and a laparotomy was performed to expose the uterus Normal saline (0 1 ml) or terbutaline (0 1 mg in 0 1 ml normal saline) was injected intramuscularly into the fetuses through the intact uterine wall After this procedure the laparotomy incision was closed The whole operation never took more than 10 min The animals recovered and 3 h later the does were again anesthetized with ether and the uterus exposed through the same incision In another control group the does were operated only once and no fetuses received any injections

In all cases a ligature was tied around the upper part of the vagina and the intact uterus was removed and immersed in normal saline at room temperature Immediately after delivery of the fetuses a ligature was tied around the umbilical vessels and the neck to prevent spontaneous breathing

The litter size varied between 5 and 13 and the fetal weights between 35 0 and 53 5 g

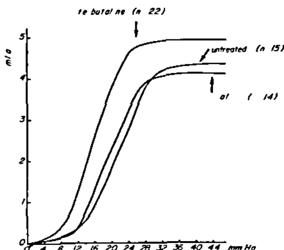


Fig 1 Inflation pressure volume curves in fetal rabbit lung at 28 days of gestation Comparison between terbutaline treated saline treated and untreated

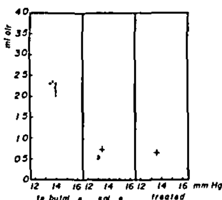


Fig 2 Pressure volume relationships at inflation of air in fetal rabbit lung at 28 days of gestation Comparison between terbutaline treated saline treated and untreated animals in the pressure interval 12 0–15 9 mmHg

Excluded were three does with premature spontaneous delivery before the second laparotomy Also excluded were fetuses where the period between the second laparotomy and the experimental procedure exceeded 3 h and fetuses where technical errors occurred during preparation The trachea of the fetuses was exposed and a cannula was inserted The cannula was connected to a syringe and a pressure transducer (Statham P 23 BC) in an air tight system and pressure curves were recorded by a Grass Polygraph (model 7) Pressure volume curves of the lungs were established using inflation with air into the intact fetuses Pressure readings at different levels were registered after one minute of equilibration and maximum pressures were noted at the bursting of the lungs For each of the fetuses 5–10 steps of inflation were made Recording was performed in all animals within 3 h after death an interval reported not to change the pressure volume curves (11)

Statistical evaluation was carried out by Student s *t* test and Fisher s permutation test followed by the Edgeworth distribution *P* values less than 0 05 were considered as statistically significant

RESULTS

The mean inflation pressure curves at 28 days of gestation for 22 terbutaline treated 14 saline treated and 15 untreated animals are shown in Fig 1 The curves of the saline and untreated groups are approximately equal In the terbutaline group there is a shift to the left and a larger maximum volume is achieved

The pressure volume relationships in different pressure intervals are presented in Fig 2 and Table 1 Significantly higher volume recordings were noted in the terbutaline group compared to the two control groups except in the interval 28 0–31 9 mmHg where the difference was not statistically significant compared to the untreated group

Table I *Pressure volume relationship in differ... pressure intervals in fetal rabbit lung*
Mean ± S E M

Pressure interval	Terbutaline	Saline	Untreated
4 0–7 9 mmHg			
mmHg	5 71±0 23	6 12±0 18	6 04+0 ...
ml air	0 17±0 02	0 10±0 01	0 12+0 0...
n	19	14	15
8 0–11 9 mmHg			
mmHg	9 64±0 14	10 18±0 24	10 52 0...
ml air	0 58±0 07	0 23±0 01	0 23+0 0...
n	22	9	12
12 0–15 9 mmHg			
mmHg	13 74±0 16	13 11±0 20	13 60+0...
ml air	2 01±0 15	0 64±0 04	0 64 0...
n	22	14	15
16 0–19 9 mmHg			
mmHg	17 50±0 0	17.58±0 34	18 17+0
ml air	3 57±0 18	1 88±0 04	1 52 0
n	18	13	13
20 0–23 9 mmHg			
mmHg	21 08±0 17	21 70±0 34	21 65 0...
ml air	3 58±0 26	2 79±0 15	2 19 0
n	10	10	10
24 0–27 9 mmHg			
mmHg	25 20±0 49	25 22±0 33	25 71+0
ml air	4 27±0 31	3 26±0 26	3 31+0
n	5	7	12
28 0–31 9 mmHg			
mmHg	30 90±0 24	29 25±0 75	29 25+0
ml air	4 72±0 25	3 40±0 40	3 77+0
n	5	2	4
32 0–40 0 mmHg			
mmHg	36 05±0 79	36 45±0 80	38 00+1
ml air	4 88±0 23	3 69±0 19	3 74+0
n	11	11	5

Significance indicated versus the terbutaline g... $p<0\ 05$ $^{b}p<0\ 01$ $p<0\ 005$ $^{d}p<0\ 001$ versus the ... group $p<0\ 05$ $^{f}p<0\ 01$

The mean transpulmonary pressures in the ... intervals were found to be equal or signific... lower in the terbutaline group compared to the control groups except in the intervals 1? 0... mmHg and 28 0–31 9 mmHg where the mean ... sure were slightly lower in the control groups ... adjust for this difference in mean pressures ... statistical evaluation of inflated volumes ... observations of the terbutaline and saline gro... the interval 12 0–15 9 mmHg were divided into ... groups and analyzed by Fischer s permutation ... Following this correction a significantly gr... volume was found in the terbutaline group f... interval 28 0–31 9 mmHg no such evaluation c...

ıade because of the small number of observa

ımparing the two control groups a significantly er volume was found in the saline group in the vals 16 0–19 9 mmHg and 20 0–23 9 mmHg ough the mean pressures recorded in these in als were equal In all other intervals no signifi differences were found in volume or pressure een the two control groups

ıe mean fetal weight in the terbutaline group 43 7±1 2 g (mean ±S E M) in the saline p 47 6±1 5 g and in the untreated group ±1 0 g No significant differences were found een the mean weights of the groups

DISCUSSION

he last part of gestation the mammalian lung rgoes rapid maturation During this period in sed amounts of elastic tissue and alveolar tures appear in the fetal lung Parallel to this lopment there is an increased formation of actant from type II cells of the alveolar lining In 1969 Liggins observed that lambs delivered r prenatal glucocorticosteroid administration viable before pulmonary surfactant would nally be present in amounts sufficient to ilize the alveoli These results suggested that maturation in some way had been accelerated Other investigators showed that administra of corticosteroids into rabbit fetuses two to e days before preterm delivery resulted in an lerated appearance of alveolar surfactant (9 Similar results have also been reported in *in* experiments (15) An increased lung volume at transpulmonary pressure in fetal rabbit has also ı demonstrated after isoxuprine administration e days before term The phenomenon was ıd already 3 5 h after injection of the drug (17) authors suggest that the mechanism of this action might be an enhanced release of

rabbit fetuses pulmonary surfactants are de ıle at day 24 and increase markedly as preg ı procedes (7 10) At 28 days of gestation the ogical maturation in all parts of the fetal lung is known to be completed (10) Previous nave shown that the volume of air present at transpulmonary pressures correlates well to parameters of measuring alveolar surface ac l (5)

In our experiments we have used a β_2 receptor stimulating drug terbutaline with known selective bronchodilating and uterine relaxing properties in jected at day 28 of gestation into rabbit fetuses An increased air volume capacity was found in the terbutaline treated animals at equivalent low trans pulmonary pressures in all intervals as compared to the controls Interesting to note was also the pres ence of a significantly higher volume at equivalent pressures in the interval 32 0–39 9 mmHg where several of the maximum pressures occurred indi cating an increased total lung capacity after terbutaline treatment

Comparison between the two control groups re vealed a significantly higher volume in the saline treated group at equivalent mean pressure in the intervals 16 0–19 9 mmHg and 20 0–23 9 mmHg As differencies in lung volume were noted only in these two intervals it is doubtful if a stress factor like a second laparotomy has any effect on the pulmonary distensibility in fetal rabbit lung

Although surfactant mediated effects probably account for the shift in the pressure volume rela tionship after β mimetic stimulation there are also other possible mechanisms of action as alteration in tissue elasticity or relaxation of the bronchial smotth muscle cells

Our experimental evidence should therefore be supplemented with a direct determination of the amount and properties of the surface active material in the alveolar lining layer

ACKNOWLEDGEMENTS

This research was supported by the Swedish State Medi cal Research Council (No 2464) and Expressens Pre natalforskningsfond The reading and revising of the man uscript by Professor N Wiquist and Assistant Professor I Kjellmer is gratefully acknowledged The authors also wish to thank AB Draco Lund Sweden for generously supplying terbutaline sulfate

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Submitted for publication March 10 1977

Thomas Hedner
Department of Pharmacology
Fack
S-400 33 Goteborg 33
Sweden

Acta Obstet Gynecol Scand 57 327–331 1978

THE EFFECTS OF LONGACTING PARACERVICAL BLOCK ANESTHESIA ON THE ABORTIFACIENT EFFICACY OF INTRA AMNIOTIC PGF_2 AND HYPERTONIC SALINE

M I Ragab [1] D A Edelman and L Laufe

From the [1] Ain Shams Universit Cairo Egypt and the [2] Internati nal Fertility Research Program Research Triangle Park N C USA

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il recently when prostaglandin F_2 (PGF) be e commercially available for intra amniotic use the instillation of hypertonic saline augmented with intravenous oxytocin was the most widely used procedure for midtrimester abortion Several studies (1 3 4 5) have indicated that effective intra amniotic PGF dose schedules may be safer than the intra amniotic administration of hypertonic saline with or without oxytocin augmentation However vomiting diarrhea and pelvic pain are more frequent with effective PGF_2 methods (2) The administration of antiemetics and antidiarrheal agents may attenuate vomiting and diarrhea A re cent report from CDC challenges the concept that saline produces a higher complication rate (8) One must remember that all cases in this study were from the U S A Racial characteristics may contri bute to the variations in results generated in interna tional trials (10)

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le I *Side effects and complications of PGF_2 and saline with and without paracervical block anesthesia*

	PGF		Saline	
ffect/complication	No PCB (N=49) (%)	With PCB (N=50) (%)	No PCB (N=50) (%)	With PCB (N=49) (%)
ng	24 5	8 0	0 0	0 0
	28 6	12 0	0 0	0 0
	6 1	0 0	0 0	0 0
>38°C)	0 0	0 0	1 0	8 ?
laceration	4 1	0 0	4 0	0 0
	0 0	0 0	0	? 0

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I Side effects and complications of PGF$_2$ and saline with and without paracervical block anesthesia

	PGF$_2$		Saline	
mplication	No PCB (N=49) (%)	With PCB (N=50) (%)	No PCB (N=50) (%)	With PCB (N=49) (%)
ng	44 5	8 0	0 0	0 0
	28 6	1 0	0 0	0 0
	6 1	0 0	0 0	0 0
>38°C)	0 0	0 0	1? 0	8 ?
laceration	4 1	0 0	4 0	0 0
	0 0	0 0	? 0	0

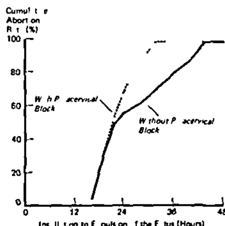


Fig 1 Cumulative abortion rates for the 40–20 mg intra amniotic prostaglandin F_2 dose schedule with and without paracervical block anesthesia

tional 20 mg PGF_2 after 24 hours if abortion had not yet occurred and (2) 200 ml of 20% hypertonic saline augmented with intravenous oxytocin

METHODS AND MATERIALS

From April to September 1976 a comparative study was conducted to assess the effects of serial longacting paracervical block anesthesia on the abortifacient efficacy of intra amniotic $PGF_{2\alpha}$ and hypertonic saline augmented with intravenous oxytocin for aborting patients at 16 to 20 weeks gestation

Abortion procedures

Patients were aborted with 1 of 2 intra amniotic techniques (1) an initial dose of 40 mg PGF_2 with an additional 20 mg after 24 hours (100 patients) and (2) 200 ml of 20% hypertonic saline without prior aspiration of the amniotic fluid augmented with low doses of intravenous oxytocin (100 patients) One half of the patients aborted by each of the above techniques received longacting paracervical blocks starting at 4 hours after the time of the initial drug instillation and repeated every 6 hours (up to a maximum of four injections) until abortion of the fetus Paracervical blocks were not given if the cervix was effaced at the scheduled time of injection The paracervical blocks were performed by injecting 5 cc of 1% lidocaine with epinephrine 1 100000 at the 4 and 8 o clock positions

For all patients the abdominal wall was sterilized and anesthetized with 1% lidocaine and the uterus was punctured with an 18 gauge needle A small amount of amniotic fluid was withdrawn to verify correct placement of the needle Prostaglandin was administered through a polyethylene catheter threaded through the needle A test dose of 5 mg PGF_2 was administered over a 5 min period and an additional 35 mg was injected over the next 5 min if there were no adverse reactions An additional 20 mg PGF_2 was administered if abortion did not occur within 24 hours unless there was uterine bleeding ruptured membranes or cervical effacement or dilation

A maximum of 200 ml 20% hypertonic saline slowly instilled through a transabdominally placed c ter over a period of at least 5 min If during the tim syringe was being refilled there was a marked ref fluid from the catheter no additional saline administered The mean amount of saline instilled w ml the range was from 150 to 200 ml

Following instillation all patients received only mependine hydrochloride intramuscularly

Two hours after the initial PGF_2 instillation, pa received an IV drip of a 5% dextrose solution at a ra ml/minute At the onset of labor pains patients m with hypertonic saline were administered a consta travenous infusion of oxytocin in a 5% dextrose so which was regulated according to uterine response a Harvard infusion pump The rate of the infusion inversely with the strength duration and frequency uterine contractions and with the condition of the c The infusion rates varied from 0 to 110 mIU/min (54 mIU/min) and reflected the differing physiologi sponses of the patients to the oxytocin After rupt the membranes and/or abortion of the fetus oxytoc infused at a rate of about 100 mIU/min

Subjects

Only healthy women without preexisting system gynecologic diseases were selected as subjects f study Patients aborted with either of the study dures were similar ($p>0$ 10) with respect to their ductive histories and other selected characteristics mean age was 33 1 years (range 22 to 44) and the parity was 3 9 live births (range 0 to 7) Four percer nulliparas 34 5% were grandmultiparas and 6 ported having a previous spontaneous or induced tion

Study design

The abortion procedures (intra amniotic PG hypertonic saline with or without paracervical anesthesia) were randomly assigned to subjects following manner Before initiating the abortio physician responsible for performing the pro

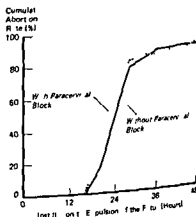


Fig 2 Cumulative abortion rate for intra amnioti with and without paracervical block anesthesia

e II *Median times (hours) from instillation to onset of labor uterine bleeding rupture of the branes and abortion of the fetus for* PGF_2 *and saline with and without paracervical block anesthesia)*

t	PGF_2 No PCB ($N=49$)	PGF_2 With PCB ($N=50$)	Saline No PCB ($N=50$)	Saline With PCB ($N=49$)
lation to labor	2 1	2 3	7 4	11 6
lation to uterine bleeding	17 3	13 8	16 1	14 6
lation to rupture of membranes	21 3	19 8	21 5	19 4
lation to abortion	22 1	21 3	24 0	2_ 7

ed a sealed envelope which specified the particular dure for the patient A second physician who was onsible for follow up care and evaluation of the pa s was kept unaware of the particular procedure used ny patient

tients were requested to return for a follow up physi xamination at about four weeks after the abortion w-up data were obtained for 97 5% of the patients

itions and criteria

ational age was calculated as the number of com d weeks from the onset of the patient s last normal strual period to the day of the abortion If the patient l to abort the fetus within 48 hours of the initial lation the trial was declared a failure and other opriate therapy was initiated The abortion was de l as incomplete when the fetus delivered without as nce but intervention was required to deliver the nta. If the patient failed to completely expel the nta within one hour of aborting the fetus the nta was removed with ring forceps

lly the significance level of statistical tests (the lue) is given

RESULTS

niocentesis could not be performed even after ated attempts in 2 patients at 16 and at 18 ks gestation They underwent hysterotomy concurrent tubal ligation and were excluded ent analyses

Among patients aborted with PGF rates of side effects were significantly lower ($p<0$ 10) for those with longacting paracervical blocks than for those without them (Table I) Between the 2 groups of patients aborted with saline there was no significant differences ($p>0$ 10) in the rates of side effects or complications (Table I) Two patients aborted with saline had cervical lacerations neither of which required repair Blood loss was less than 300 ml for all patients and no patient required blood replacement therapy

While the cumulative abortion rates were not significantly different ($p>0$ 10) for the 2 groups of patients administered saline (Fig 1) they were significantly different ($p<0$ 10) for patients administered PGF_2 with or without paracervical block anesthesia (Fig 2) The cumulative abortion rate for PGF_2 with paracervical block anesthesia was consistently higher than the cumulative rate for saline with or without paracervical block anesthesia but the cumulative rates were not significantly different ($p>0$ 10)

The median times from instillation of PGF_2 or saline to the onset of uterine bleeding rupture of the membranes and abortion were not significantly different ($p>0$ 10) (Table II) Although the median

lII *Rates of incomplete abortion with* PGF_2 *and saline with and without paracervical block (PCB)*

utcome	PGF_2 No PCB ($N=49$) (%)	PGF_2 With PCB ($N=50$) (%)	Saline No PCB ($N=50$) (%)	Saline With PCB ($N=49$) (%)
lsion of fetus and placenta	42 9	78 0	40 0	51 0
of placenta with ring forceps	55 1	20 0	50 0	40 8
on within 48 hours	? 0	? 0	10 0	8 ?

times from instillation to the onset of labor were not significantly affected by the paracervical blocks they were significantly lower ($p<0$ 10) for patients aborted with $PGF_{2\alpha}$ compared to those aborted with saline (Table II)

An additional 20 mg of $PGF_{2\alpha}$ was more often given to patients who did not receive paracervical blocks (38 8%) than to those who did (12 0%) Two patients administered PGF_2 failed to abort within the 48 hour trial period (Table III) These patients were administered intravenous oxytocin (100 mIU/min) and aborted after 72 2 and 74 2 hours Nine (9 1%) patients administered saline failed to abort within the 48 hour trial period All of these patients had signs of impending abortion (uterine bleeding) and aborted from 48 7 to 68 2 hours after the initial saline instillation

Rates of complete abortion were significantly higher ($p<0$ 10) for the $PGF_{2\alpha}$ treated subjects with paracervical block anesthesia than without paracervical block anesthesia (Table III) However for the 2 groups of patients administered saline the rates of complete and incomplete abortion were not significantly different ($p>0$ 10)

For patients who did not receive paracervical blocks meperidine (50 mg IM) was more often needed for the comfort of the patient at the time of placenta removal ($PGF_{2\alpha}$ without paracervical block 51 9% with paracervical block 20 0% saline without paracervical block 28 0% with paracervical block 0 0%)

DISCUSSION

Although the administration of longacting paracervical block anesthesia significantly improved the abortifacient efficacy of PGF_2 it did not improve the efficacy of hypertonic saline augmented with intravenous oxytocin Patients aborted with $PGF_{2\alpha}$ and who received paracervical blocks aborted sooner (98% vs 70% at 32 hours) and with lower rates of incomplete abortion and gastrointestinal side effects compared to patients *who did not receive paracervical blocks*

The mechanism by which the paracervical blocks affect the abortifacient efficacy of PGF_2 is not understood The paracervical block probably does not interact with PGF_2 directly or affect the abortifacient efficacy of PGF_2 per se but probably brings about changes in cervical compliance Extending the duration of the efficacy of the block (longacting) probably enhances its effect on cervical compliance The paracervical blocks may indirectly enhance the abortion process by alleviating pain associated with the procedure With the alleviation of pain there could be a decrease in the output of epinephrine Since epinephrine decreases uterine contractility which in turn may delay the abortion the attenuation of epinephrine output may result in higher uterine contractility and reduced instillation to abortion times Twenty four hours after $PGF_{2\alpha}$ administration 12% of the patients who received paracervical blocks compared to 38 8% who did not had cervical dilation or effacement indicating that the paracervical block anesthesia may enhance PGF_2 in causing cervical softening effacement and/or dilation Hasson (8) has reported that after topical application of lidocaine to the uterus cervical dilation may be easier and that the lidocaine may affect the internal cervical os

For patients aborted with saline the cumulative abortion rates rates of incomplete abortion side effects and complications were similar regardless of whether or not paracervical block anesthesia was used The cumulative abortion rates for patients aborted with PGF_2 and paracervical block anesthesia and for patients aborted with saline augmented with intravenous oxytocin were similar The principal disadvantage of saline augmented with intravenous oxytocin is an increased incidence of cervicovaginal fistula (7) consumptive coagulopathy (2) and the possibility of water intoxication (6) For these reasons the use of effective PGF_2 dose schedules may be preferable to the use of saline augmented with *high doses of intravenous* oxytocin

Further studies will be necessary to evaluate the effectiveness safety and advantages of using longacting paracervical block anesthesia as an adjunct to midtrimester abortion procedures These studies should include the evaluation of $PGF_{2\alpha}$ and its methyl analogues administered via the vaginal intra amniotic extra amniotic and intra muscular routes

ACKNOWLEDGEMENT

The authors thank Dr Nelson Shub for suggesting the study and for his assistance in its design

The study was supported in part by a grant from the Upjohn Company

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Submitted for publication August 16 1977

Leonard Laufe
International Fertility Research Program
Research Triangle Park
North Carolina ?7709
USA

Acta Obstet Gynecol Scand 57 333–336 1978

COMPARISON OF EXTRA AMNIOTIC INSTILLATION OF RIVANOL AND PGF_2 EITHER SEPARATELY OR IN COMBINATION FOLLOWED BY OXYTOCIN FOR SECOND TRIMESTER ABORTION

Anders Ólund and Bertil Larsson

From the Department of Obstetrics and Gynecology Karolinska institutet Huddinge University Hospital Huddinge Sweden

ct Second trimester abortion was induced in 9? s by extra amniotic instillation of Rivanol and/or followed by intravenous oxytocin after 24 hours stillations were made via a catheter with a balloon with 30 ml and left in place until abortion but never re than 24 hours Induction was started by Rivanol (n=23) PGF_2 alone (n=23) Rivanol combined PGF_2 (n=23) or Rivanol combined with half dose (n=?3) and the patients were allotted to the differ oups in a random manner The Rivanol solution was ed as a single dose but PGF_2 was instilled every ?nd or 4 hours The mean induction–abortion time was r in all 4 groups but a number of patients given , alone or in combination with Rivanol aborted r than patients induced by Rivanol alone during the l before intravenous oxytocin was administered ointestinal side effects were equally common after ol as after PGF_2 With the methods and doses used t investigation PGF_2 alone or combined with l with subsequent oxytocin had no over all ad Rivanol

or extra amniotic instillation of hypertonic e solutions for induction of second trimester has been the method most commonly used andinavia for the last two decades Although method is generally effective it may lead to even fatal complications (1 15)

Japan because of reports of maternal deaths the use of hypertonic saline solutions (15) this has been replaced by extra amniotic in ion of an 0 1% solution of Rivanol (6 9 mino-?-oxyethyl acridine lactate) It was found e equally effective as hypertonic saline and has been used in Japan for more than 20 years hout any known serious side effects (11)

ivanol has been used successfully in Sweden e 1969 (6) In a comparison of the efficacy of the ertonic saline and Rivanol methods respective Ingemanson (6) reported a shorter induction–rtion interval for Rivanol as well as the absence of serious complications In most investigations oxytocin has been used as supplementary therapy (3 5 10) and Rivanol has been used alone in only a few reports (6)

The use of prostaglandins as abortifacients was first reported in 1970 (7 14) The advantages of the method were a shorter induction–abortion interval and the absence of fatal complications A serious disadvantage however was the high incidence of gastrointestinal side effects especially when the substance was given by the intravenous route (8) This incidence has however been reduced by the use of the intrauterine route and new prostaglandin analogues (8)

The purpose of the present study is to evaluate the usefulness of Rivanol and PGF_2 administered extra amniotically either alone or combined and with subsequent oxytocin for induction of abortion with special reference to the induction–abortion interval and side effects

PATIENTS AND METHODS

The material consists of 92 apparently healthy women admitted to hospital for legal abortion on social reasons The patients were randomly distributed into four treat ment groups each consisting of 23 patients Table I gives the distribution of the age parity and number of previous legal abortions as well as the gestational age estimated from uterine size

Induction was started by the introduction of a Foley catheter No 20 via the cervical canal into the extra ovular space just inside the internal cervical orifice The Foley balloon was filled with 30 ml of physiological saline Rivanol and/or PGF was then instilled (see below) The catheter was left in place for 24 hours or expelled with the foetus if the patient aborted earlier If the abortion had not started by the following morning an intravenous infusion of oxytocin 70 I U in 1000 ml of 5 5% glucose was started This infusion was given at the rate of 1000 ml every 12 hours until abortion occurred The patients were

Table I *Distribution of age parity earlier legal abortion and gestational age*

Group	Age		0-para	X para	Earlier legal abortion	Week of gestation clinical examination		
	Mean	Range				Mean	Range	S
1 Rivanol ($n=23$)	24	14–40	7	16	6	15 1	13-19	1
2 PGF_2 ($n=23$)	24	16–34	9	14	7	16 [illegible]	13-[illegible]	2
3 Rivanol+PGF_2 ($n=23$)	25	16–41	8	15	7	17 0	13-25	3
4 Rivanol+$\frac{1}{2}\times PGF_2$ ($n=23$)	[illegible]4	15–44	10	13	5	16 4	13-[illegible]	[illegible]

closely observed throughout the procedure and side effects if any were carefully recorded

The following substance were instilled in the extra ovular space via the catheter

Group 1 Rivanol

A 0 1% solution of Rivanol was slowly instilled 10 ml per gestational week but never more than 150 ml after which the catheter was ligated at its lower end

Group 2 PGF_2

1 ml of a saline solution containing 0 25 mg PGF_2 per ml was instilled followed by 3 ml every 2nd hour for up to 24 hours At a gestational age of more than 16 weeks the dose was doubled and given at the same intervals

Group 3 Rivanol + PGF_2

Rivanol was instilled as in group 1 followed by PGF_2 as in group 2

Group 4 Rivanol + 1/2 × PGF_2

Rivanol and PGF_2 was instilled as in group 3 except for the dose of PGF_2 which was reduced by half

RESULTS

There was no significant difference in the clinical characteristics of the groups (Table I) as regards age parity number of earlier abortions and weeks of gestation (evaluated by mean of Student s *t* test and the chi square test)

The cumulative abortion rates of the four groups are graphically illustrated in Fig 1 Patients given PGF_2 (groups 2 3 and 4) in a number of cases aborted earlier than patients treated with Rivanol alone (group 1) The cumulative abortion rates from 30 hours after induction were essentially similar in all groups

The mean abortion times were in group 1 29 9 hours (range 23 9–47 2) in group 2 26 7 hours (range 8 9–63 0) in group 3 24 9 hours (range 9 3–66 1) and in group 4 26 5 hours (range 13 1–50 1) The differences in mean abortion time between any two of the four groups were statistically significant (Student s *t* test)

Table II gives the complications and side eff The small number of patients with endome excessive blood loss not large enough to war statistical comparison seems to be equally di buted among the groups Gastrointestinal side fects were common in all four groups The so what higher incidences in group 2 and 3 did differ significantly (chi square test) from thos the other two groups

DISCUSSION

The induction–abortion interval in the Ri group (group 1) of the present study (83% a tions within 36 hours 100% within 48 hours) the same order of magnitude as that given in vious reports Thus Ingemanson (6) reported within 48 hours and 94% within 72 hours and melmann et al (5) 77% within 48 hours and within 72 hours

The shorter abortion time observed in the pr study might be explained by the difference i methods used Ingemanson (6) used a catheter out a balloon and introduced it almost com into the uterine cavity after the instillatio Rivanol but did not use subsequent intravenou ytocin Himmelman et al (5) used a Foley-ca

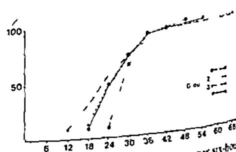


Fig 1 Percentage of patients aborting per six-hou of time

e II *Complications and side effects*

	Groups			
	1 Rivanol (n=23)	2 PGF₂ (n=23)	3 Rivanol+ PGF₂ (n=23)	4 Rivanol+ ×PGF₂ₐ (n=23)
metritis	2 (8 7%)	1 (4 4%)	3 (13%)	3 (13%)
loss with transfusion	1 (4 4%)	2 (8 7%)	2 (8 7%)	3 (13%)
ointestinal side effects				
tal	12 (52%)	16 (70%)	16 (70%)	13 (57%)
usea	7 (30%)	13 (57%)	13 (57%)	8 (35%)
miting	10 (44%)	11 (48%)	9 (39%)	12 (52%)
rrhoea	0	2 (8 7%)	0	1 (4 4%)

pped with a balloon filled with only 10 ml one l of the volume used in our study and ad stered oxytocin at 24 and if necessary at 48 s

hat the presence of a balloon catheter reduces induction–abortion interval has been demon ted by Fylling & Refsdal (3) Moreover Manabe induced abortion with only a metreurynter d with 150 ml saline solution followed by in uscular injection of oxytocin With the aid of a hod similar to that used by Manabe except for use of a balloon catheter filled with only 40 ml responding results have been obtained by Ölund oth Brandel (to be published) These observa s emphasize the importance of the balloon per h the induction of abortion

he underlying mechanism of the abortifacient ct of Rivanol is still obscure An oxytocic effect elated acridin dyes has however been reported Furthermore in abortions induced with hy tonic saline a stimulation of the release of en enous $PGF_{2\alpha}$ from the decidua has been pro- ed by Gustavii (4) A similar release of PGF_2 in tion induced by Rivanol was suggested by n et al (12) In the present investigation the initial lag time and the high incidence of ntestinal side effects after induction with ol lend support to such a possibility

material the method including only PGF_2 uced abortion in 48% within 24 hours and in within 36 hours (Fig 1) figures resembling achieved with comparable methods Embrey al (2) for instance adding oxytocin after 36 noticed 67% abortions within 24 hours and within 36 hours

In the present study PGF_2 alone or combined Rivanol induced abortion within 24 hours more than Rivanol alone (Fig 1) Regarding the abortion rate after 24 hours when oxytocin was added the results of induction with PGF_2 com bined or alone showed no benefits over the abor tion rate with Rivanol Furthermore the PGF_2 methods involves repeated instillation of the drug a risk of cervico vaginal injuries (13) and bron choconstriction (16)

Even if there is a initial lag time of approximately 24 hour in the Rivanol method the mean abortion time is not significantly longer than in the PGF_2 methods

Rivanol has also few if any contraindications and there has been no reports of cervico-vaginal injuries with the doses used in the present study

Judging from the observations made in the pres ent series the use of the Rivanol method as applied here means a safe as well as a simple way for induction of midtrimester abortion It would appear that PGF_2 alone or combined with Rivanol with subsequent oxytocin after 24 hours as used in the present study had no definite over all advantage over the Rivanol method

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Submitted for publication May 24 1977

Anders Ölund
Department of Obstetrics and Gynecology
Huddinge University Hospital
S 141 86 Huddinge
Sweden

Acta Obstet Gynecol Scand 57 337–348 1978

ULTRASTRUCTURE AND VARIATIONS OF HUMAN CERVICAL MUCUS DURING PREGNANCY AND THE MENOPAUSE

F C Chretien

Laboratoire d'Histologie – Embryologie – Cytogenetique Hopital de Bicetre France

ract Ultrastructural aspect and variations of cervical s have been studied by scanning electron mi opy in 58 pregnant and 29 menopausal women In groups a striking tightening of the ultrastructural protein framework was demonstrated The omenon appears to occur very rapidly at the begin of pregnancy while patients near the menopause more variable patterns The results are compared to nown evolution of cervical mucus ultrastructure dur he ovarian cycle and discussed from a rheological of view Particular attention was paid to the eventual acterial role of cervical mucus in pregnancy which found to be very plausible

ng pregnancy the uterine cervix undergoes ortant physiologic changes under hormonal in nce The most striking modification occurs in endocervical mucosa and glands At the epi ial level a cellular proliferation is manifested by erous areas of active cell multiplication and by stratification of the tall columnar cells (12) The ds grow larger become gradually more numer and more active as pregnancy proceeds Occa ally hypertrophy and hyperplasia are extreme glandular stroma becomes oedematous and se and it would appear that there is lessened port for the glands

se though rather small amounts of cervi mucus can be sampled during that period the secretion is noticeable from the beginning the end of pregnancy (13) In addition no icant variation can be observed in secretion ince dependent on the number of children or of pregnancy (3) However during preg y the cervical mucus undergoes drastic varia modifying both its physico-chemical pro- ies and its physical appearance

a macroscopic point of view cervical during pregnancy is known to become ly thick sticky and gelatinous therefore simi lar to that seen pre menstrually during the time of normal luteal activity (2) Thus appears at the exter nal os a clot of dense mucoid material which ob- structs the cervical canal The physiological signifi cance of this mucus thickening which causes an important decrease of its spinability has not yet been established However bacterial invasion of the uterine cavity during pregnancy is known to be extremely rare Beck (1) stated that thick cervical mucus in the canal during pregnancy aids in pre venting the ascent of pathogenic bacteria into the uterine cavity The fact that the tightening of cervical mucus framework could create a physical barrier to the largest bacteria is now made more plausible by the most recent information on cervical mucus ultrastructure Due to its depth of field the scanning electron microscope can provide a three dimensional view of the spatial arrangement of the infrastructure of cervical mucus and shows it as a meshwork of intertwined filaments (8) stretching or thickening during the ovarian cycle depending on hormonal influence (7) Indeed progesterone is known to cause the mucus to thicken whereas oestradiol has the opposite effect The results given in a preliminary report have shown that cervical mucus during pregnancy and after the menopause can have an ultrastructural appearance similar to that described for the late luteal period (6) The important thickening of cervical mucus could be due to the shrinkage of its infrastructure under the effects of progesterone domination during the same periods

The following study with the scanning electron microscope was carried out in order to provide further information on the variations of cervical mucus framework throughout pregnancy and during the menopause Particular attention was paid to the possible mechanical antimicrobial role of cervical mucus during pregnancy

Table I

Gestation duration	Number of cases: Primi gravidas 27	Multi gravidas 31
3 weeks to 1 month	3	4
5 weeks	4	3
2 to 3 months	5	4
5 to 6 months	3	4
7 to 8 months	4	5
8½ months	4	5
Last week of pregnancy	4	6

METHODOLOGY

In both pregnant and menopausal patients mucus samples were secured from cervices that were apparently healthy *and did not reveal obvious erosions The cervix* was exposed with a speculum in a good light and the ectocervix gently wiped with sterile gauze to carry away vaginal debris and old mucus The mucus was taken by aspiration by means of a plastic Braun probe adapted to a 10 ml disposable syringe After the external opening had been cleaned with cotton the probe was introduced into the cervical canal The mucus was then aspirated very carefully in order to avoid the formation of bubbles which could create alterations in the native structure of the sample Only those specimens which had not been submitted to strong suction or ejection were set aside for observation At least two samples per donor were taken

The mucus was placed on glass coverslips then prepared for scanning electron microscopy including freeze drying according to the procedure described previously in a detailed technical paper (5) The samples were coated with either pure gold or an alloy of 80/20% goldpalladium

Scanning observations were conducted with Cambridge Stereoscan Mk II and Etec Autoscan Microscope under an accelerating voltage of 25 and 20 kV respectively

RESULTS

Pregnancy

The mucus specimens used for this study were taken from 58 pregnant patients between 19 and 39 years of age distributed between primigravidas and multigravidas with a gestation range from 3 to 38 weeks (Table I)

The observation of 153 mucus samples showed that the filamentous woof constituting its solid phase persists throughout the pregnancy Indeed during this period the observed ultrastructural organization of cervical mucus appears to be not fondamentally different from certain aspects described in the mucus sampled during the cycle out of the ovulatory period (7)

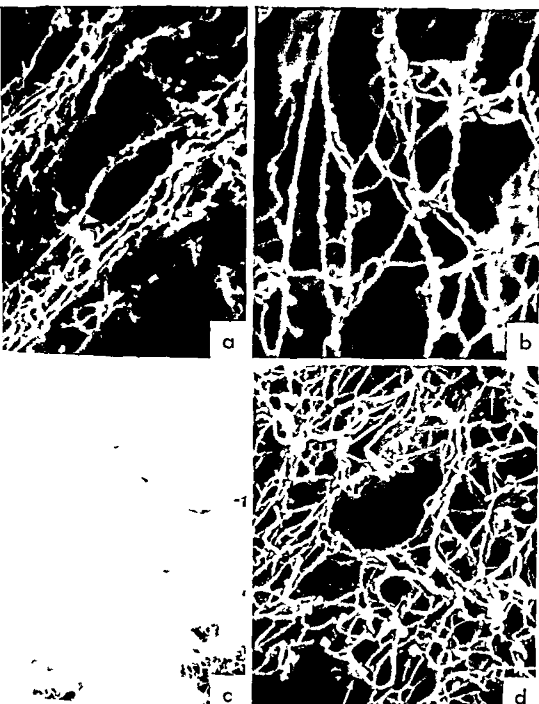
The same types of filaments can framework with the exception of the t ments (α type) which are absent to the end of pregnancy *In addition* revealed an obvious evolution as ceeds of both the length and aspect of the filaments as well as in the dimension of t they constitute

In order to present the results m pregnancy was divided into 6 periods 3 weeks 2½ months 5–6 months 7–8 week of pregnancy This sequence wa from the fact that the differences are cant from one month to the following in t part of pregnancy Therefore there was nc analyse each of the nine months o characteristic aspects of each of the will be described in succession

3 weeks At the beginning of pregnancy mucus framework appears grossly similar to seen at the beginning of the lutheal p filaments are largely predominant and γ *only occasional The woof frequently* and shows filaments which can be smooth of their length but also show median and expansions They can form meshes of l sion (up to 7 μm) and may appear 1*b*) The mucus frequently shows an i heterogeneity of the woof density areas it is possible to find some sports framework more dense forms meshes of dimensions (Plate 1*a*)

5 weeks Two weeks later the general the framework is not greatly different t heterogeneity can be demonstrated in th the largest meshes may *attain 6 μm* (Plate However as compared with the preceding the median thicknesses puffing up certain f appear larger and areas of obvious compact be seen here and there in the sample (Plate 1*d*

2½ months This time is an important stage *evolution of the cervical mucus framework dur* pregnancy Indeed if meshes of appreciable s can be observed in the thin marginal area of sa ples the most part of the woof appears now der and homogenous (Plate 2*a*) Most of the β filame have considerably shortened and appear to roughly rectilinear The γ filaments are still oc sional and only visible in few places Lateral s



1 (a) 19th day of pregnancy The woof in which hes can be seen appears heterogenous ×10800 day of pregnancy detail showing large meshes c) 5 weeks of pregnancy At low magnification the woof heterogeneity appears particularly evident ×4800 (d) 5 weeks of pregnancy Detail showing straight and buckled filaments some of which appear puffed up by median thicknesses (arrows) ×10700

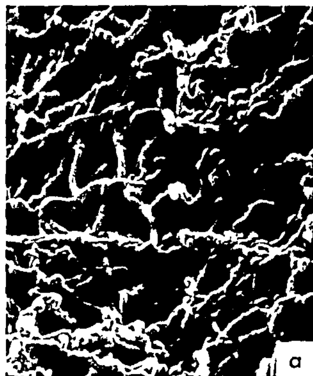
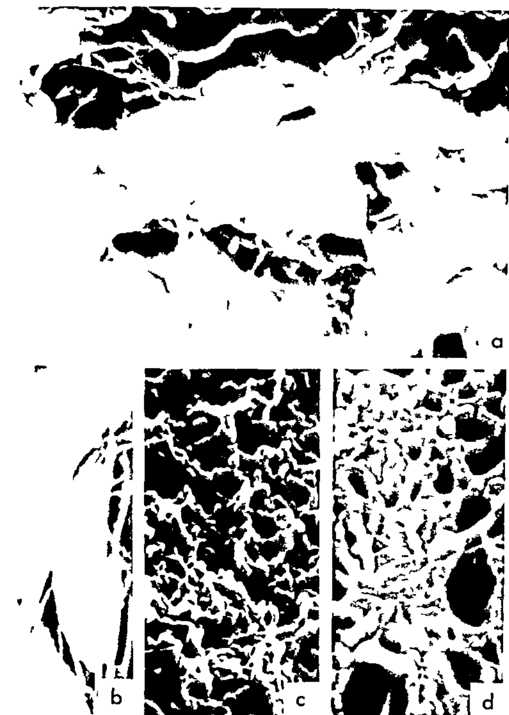








Plate 2 (*a*) 2½ months of pregnancy The woof appears considerably tightened ×10 000 (*b*) 2½ months of pregnancy Detail showing the deformed filaments and a characteristic clot (arrow) ×22 000 (*c*) 5 months of pregnancy Low magnification showing the homogeneity the woof at that stage ×4 000 (*d*) 5 months of pregnancy Detail ×11 500



3 (a) 8 months of pregnancy Detail of the structural woof in which several clots are visible (ar ×1700 (b) Last weeks of the pregnancy In this cular case cervical mucus presented in certain areas pical preovulatory aspect Note the long and smooth filaments ×13000 (c) Last week of the pregnancy In most cases the mucus framework appears to be extremely dense ×10800 (d) Last week of the pregnancy Detail Most meshes can scarcely be distinguished ×_1400

Table II

Pregnancy	3 weeks	5 weeks	2½–4 months	5–7 months	8 months	Last week
Density of the woof (+ to +++++)	+–	++	++++	++++	+++–	+++++
Appearance of filaments						
Smooth	++	++	0	0	0	0
Buckled	++	++	0	0	0	0
Straight	+	+	++	++	++	++
Puffed up	+	+	++	++	++	++
With clots	0	0	+	+	+	++
Types of filaments						
α	0	0	0	0	0	0
β	+++	++++	+++++	+++++	+++++	+++++
γ	++	++	+	+	+	+

median expansions are frequent along the β filaments which can also be expanded by clots (*Plate 2b*) The mesh dimensions which are difficult to measure rarely exceed 1 5 μm No really significant variation can be observed until 5 months

5–6 months During this period the mucus framework is particularly dense and compact (Plate 2*c*) The filaments appear very short and puffed up by successive median or lateral expansions (Plate 2*d*) The γ filaments extremely rare can be seen here and there through some of the meshes formed by the β filaments The dimension of the meshes which are very homogenous rarely goes beyond 1 3 μm Until the end of the seventh month the mesh work shows only slight variations in amplitude thought to be of little significance Thus the general aspect of the woof between 5 and 6 months of pregnancy is not fundamentally different and it is difficult to even distinguish between these different stages

7–8 months In approximately 50% of samples the framework of cervical mucus sampled in the 8th month of pregnancy seems to be a little less homogenous than previously The woof is still compact but in some places the β filaments constituting the main part of the meshwork can appear to be slightly slackened The median and lateral expansions frequent in the dense parts of the woof are here rather rare giving the filaments an almost smooth appearance (Plate 3*a*)

Last week of pregnancy The framework of cervical mucus sampled durin the last pregnancy is generally conspicuous for its compactness (Plate 3*b*) Indeed the mes appear so closely tightened that they give which looks fairly uniform the aspect of rough concrete (Plate 3*c* *d*) Due to this density of the woof most of the meshes exceed 0 3 μm The filaments are so puffed and deformed by expansions and that they may blend and constitute clots at the surface of the woof However in the mucus framework was shown to be ous in some places distributed at the p the sample the filaments appeared s elongated (Plate 3*b*) In these cases the framework was similar in appearance to th preovulatory period Nevertheless that ki rangement seems to be very rare and h

Table III

Pre menopause	1½ to 3 months between the two last menses
Menopause	4 to 6 months between the two last menses
Post menopause I	7 months to 4 years sin e the last menses
Post menopause II	More than 4 years since the last menses

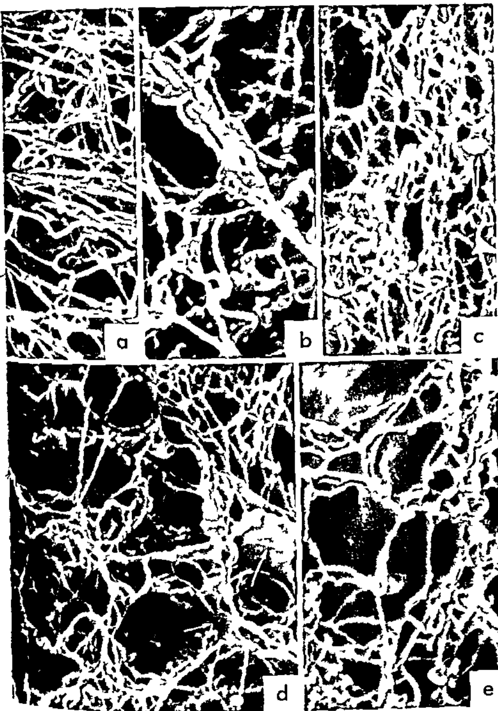


Fig. 4 (*a*) Premenopause (48 years old) Mucus sampled the 1 th day of a 36-day cycle The framework has a ovulatory appearance ×6300 (*b*) Premenopause (45 years old) Mucus sampled on the 26th day of a 30-day cycle Note that the filaments are arranged in a luteal type ×0300 (*c*) Premenopause (47 years old) Mucus sampled on the 17th day of a 45 day cycle The meshwork appears here to be very dense Some clots are protruding at the surface (arrows) ×5000 (*d*) Menopause (49 years old) 4 months since the last menses period Some clots are clearly visible (arrows) ×10700 (*e*) Menopause (same sample) Detail of particularly large meshes ×11400

Table IV

	Pre menopause	Menopause	Post menopause I	Post Menopause II
Density of the woof (+ to +++++)	Variable from + to ++++ according to stage of the cycle	+++	++++	+++++
Appearance of the filaments				
Smooth		0	0	0
Buckled		0	0	0
Straight	idem	++	++	++
Puffed up		++	++	++
With clots		+	++	++
Types of the filaments				
α	+	0	0	0
β	++++	++++	+++++	+++++
γ	++	+	+	+

considered occasional The most striking differences occurring into cervical mucus framework during pregnancy are summed up in Table II

Menopause

The mucus specimens were sampled from 29 women between the age of 45 and 69 years coming to the hospital for routine examination The patients were divided into 4 groups according to the stage of menopause (Table III) A total of 64 samples was observed

As was shown during pregnancy after the onset of the menopause the infrastructural woof of cervical mucus appears to be comparable to that described for the early luteal phase Then the meshwork tightens very rapidly to form a more and more compact structure

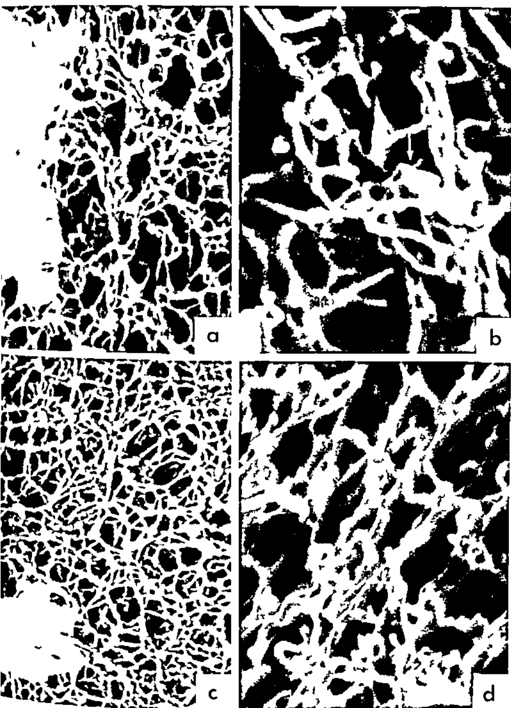
Pre menopause Generally the ultrastructural appearance of cervical mucus sampled at the beginning of the menopause appears to depend on the stage of the cycle at the time of sampling Indeed near midcycle filament arrangements resemble those of normal ovulatory type (Plate 4*a*) Whereas samples taken at the beginning or the end of cycle exhibit a tight meshwork similar to that of normal follicular or luteal phase (Plate 4*b c*)

However in most samples the woof density can exhibit a certain heterogeneity which does not seem to be related to the day of sampling For instance in a luteal type mucus one can find some [illegible] where the filaments appear smooth and even b[illegible] led The dimension of the meshes is thus very [illegible] versified and may vary between 8 and 0 5 [illegible] α filaments are absent and γ filaments only [illegible] sional

Menopause The framework is now more [illegible] and rather homogenous It is composed of s[illegible] and thicker β filaments Most of these fi[illegible] appear to be smooth and roughly rectilinear (P[illegible] 4*d e*) but they can form some clots protrud[illegible] the surface of the woof (Plate 4*d*) The mesh [illegible] mension rarely exceeds 2 5 µm

Post menopause I The most part of the [illegible] work appears to be particularly tight (Plate 5*a*[illegible] woof is now composed of very short β filam[illegible] which are frequently distorted by median nod[illegible] clots originating from lateral buds (Plate 5*b*) T[illegible] size of the meshes may vary between 1 5 and [illegible] µm

Post menopause II The woof is now unifor[illegible] so dense that most meshes can scarcely be di[illegible] guished The filaments exhibit numerous media[illegible] swellings and lateral buds Large clots are not ra[illegible] The mesh may attain 0 8 µm but the main dime[illegible] sion does not exceed 0 3 µm To make the resu[illegible] more clear the most characteristic data concern[illegible] the evolution of the cervical mucus framework du[illegible] ing the menopause are summed up in Table IV



*5 (a) Over menopause I (53 years) One year since last menses period The woof appears *to be consider* tightened as compared with the preceding stage 00 (b) Over menopause I (51 years) 3 years since the menses period Detail showing the compactness of the The arrow indicates a typical clot ×?0800 (c) Over menopause II (69 years) 19 years since the last *menses period* The woof is extremely *dense* ×10800 (*d*) Over menopause II (6 years) 15 years since the last menses period Note the extreme compactness of the meshwork × 0500

DISCUSSION

The importance of cervical mucus in human female reproductive physiology makes it essential to study its macromolecular organization and identify the mechanisms that modify this organization during the various parts of sexual life The scanning electron microscope seems incontestably to be now the best available instrument for the study of the three dimensional infrastructure of mucoid secretions but the interpretation of the pictures obtained remains particularly delicate Indeed preparation of cervical mucus for observation within a vacuum chamber must surmount several technical barriers Probably the most important is to eliminate free water contained in the specimen so that it will not vaporize under the high vacuum of the specimen chamber of the microscope In fact eliminating the important amount of water or cervical mucus (up to 95%) without inducing major changes in the native structure of such a plastic material can be considered as a challenge

Since the SEM studies of cervical mucus are very recent it is logical to ask if the data they provide are reliable The stage of fixation and dehydration are notably prone to produce many possible artifacts and one may ask whether the micrograph patterns produced on cervical mucus are really natural structures I refer the interested readers to a detailed paper devoted to the technical problems involved in cervical mucus preparation and observation under SEM (5)

Due to its great plasticity cervical mucus ultrastructure may undergo local rearrangement as a result of local accidental physical constraints Thus parameters such as mesh dimension length mean number per unity of surface of a certain type of filament cannot be measured accurately Therefore in Tables II and IV symbols such as + or − have been used instead of numbers for permitting quantitative evaluation

Although the infrastructural framework is probably altered by preparative procedures there is in fact much evidence that the pictures obtained can be considered the most faithful illustration of the natural arrangement of the structural woof in cervical mucus

Several arguments can be proposed in support of that view At first the structures described previously for the human ovarian cycle resembled none of the characteristic artifacts of which we are aware in scanning electron microscopy The parallel between their variations in the course of the cycle and the theoretical variations proposed by Ode… (18) on the basis of nuclear magnetic reson… studies (17) appears too close to be simple result of chance

Moreover being able to produce at will ovula…tory and luteal type pictures in … of castrated baboons by injecting oestrogen … progesterone (9) clearly shows that the observed structures lie in hormonal stimulation and cannot result from technical manipulation Finally the results obtained with mucus sampled from women during pregnancy and during or after the menopause corroborate the data of … observation and also correspond to the modifications of mucus framework one can logically expect from the hormonal balance during these periods

Following conception the obstruction of the cervical canal by a clot of very thick mucus appears to be a very rapid phenomenon The abrupt changes leading to the formation of an extremely … mucus framework are consistent with the … that cervical mucus during pregnancy acts as … effective filter in less than 10 weeks the mucus woof becomes similar to that of the late luteal phase thus creating a physical barrier to sperm cells (19) The density of the woof then … reaches a maximum with only slight variations … amplitude thought to be of little significance

The question arises now whether cervical … during pregnancy is able to protect the uterine cavity from microbial invasion ascending from the … Among women of normal fertility the … small number of infections of the upper genital … indicates that besides the reticulo-humoral defence mechanism there may exist a physical obstacle located in the uterine cervix which prevents bacterial and fungal invasion from the vagina It is reasonable to envisage a cervical mechanical barrier On the basis of my observations I can assume that such mechanism is highly probable It is well known that during pregnancy the penetration of cervical mucus by sperm cells is restricted The sperms are … mobilized (19) Of course due to the size of … meshes only largest bacteria or fungi could be stopped mechanically by the weft However the super imposition of many layers of meshes presents to large microbial agents a series of obstacles … which they finally become trapped

Thus after some weeks of pregnancy cervic…

s could act as an effective filter making impos the ascent of bacteria and fungi towards the ie cavity Probably the antimicrobial action of .al mucus during pregnancy does not take only by the rapid tightening of the meshwork d other mechanisms are likely to interfere g pregnancy cervical mucus has been shown ntain histiocytes plasmocytes eosinophil and ucleate cells which probably contribute to the acterial protection of the uterine cavity (3) particular arrangement of altered histiocytes olynucleate cells on the periphery of stretched cal mucus and the fact that the central zone ins many normal and healthy cells is probably ed with the antimicrobial defense of the uterine y during pregnancy

oreover the presence of muramidase (or zyme) in cervical mucus of pregnant woman likely also contributes to that defence Indeed enzyme probably secreted by the endocervix been shown able to hydrolyze the wall of both positive and negative bacteria (11) and thus d facilitate their phagocytosis inside cervical us (3 14)

uring the first third of pregnancy in certain rs of the same sample the weft appears more e than in the others This heterogeneity proba corresponds at the ultrastructural level to that h one can sometimes observe visually when suring the cervical mucus spinability with an matic device (10) Indeed cervical mucus sam at the beginning of pregnancy can exhibit one everal nodosities of different viscosity Proba during this period cervical mucus consists of a ture of chemically different forms which are pro- ed simultaneously by different cervical glands the case during the ovulatory cycle (20)

he rapid tightening of the ultrastructural woof in beginning of pregnancy is not surprising In fact ical mucus contains a smaller amount of water ng pregnancy than during the luteal phase (16) spinability is known to be dependent on water tent

ery likely the tightening of the mucus nework can be accounted for by a particular ological property of cervical mucus during pre ncy that property plasticity enables cervical cus to be deformed continuously and permanent without rupture (4) It is characteristic enough to mit diagnosis of pregnancy in 96% of 155 mucus nples (21)

Cervical mucus of menopausal women before estrogen therapy was known to have scanty ap pearance to be highly viscous or crumbly in char acter cloudy white or yellow and to have a heavy content of epithelial cells and leucocytes More over it has been shown to be impenetrable by spermatozoa in vitro (22) The considerable tighten ing of the mucus framework demonstrated by scan ning electron microscopy can evidently account for that latter property The preovulatory aspect pre sented by cervical mucus in some early menopausal patients must not be considered surprising oestrogenic analyzes made during the first few months after the menopause may show values similar to those obtained in women in child bearing age (2) In fact senile retrogression of the ovaries is apparently first attended by cessation of corpus luteum function and later by decreased estrogenic secretion

Thus concerning both pregnancy and menopausal cervical mucus scanning electron microscopic observations fully corroborate at ultrastructural level the known macroscopical data They also explain or demonstrate some of their supposed physiological properties One can state now that scanning electron microscopy has proved itself a particularly useful instrument for reproduc tion research whose performance complements that of the transmitting electron microscope It also opens a new field of research for the study of mucoid materials whose essentially lacunar or fibril lary nature may make observation impossible with the classical electron microscope

ACKNOWLEDGMENTS

Original research of this kind could never be done without the help and advice of senior clinicians I wish to ack nowledge the help of Professor P Engelmann (Hopital Lariboisiere) and Doctor J Cohen with the collection of cervical mucus samples For his very valuable criticism I am indebted to Professor G David (Hopital de Bicetre) My thanks are also due to Doctor S Segal for his kindness in making available the excellent facilities of the Popula tion Council (Rockefeller University New York) and to Professor M Bessis for kindly permitting the use of the scanning electron microscope of the Institut de Pathologie Cellulaire Inserm U48 (Hopital de Bicetre)

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Submitted for publication Febr 21 1977

F C Chretien
Histologie Embryologie-Cytogénétique
Centre Hospitalo universitaire de Bicetre
78 Avenue du Général Leclerc
94270 Le Kremlin Bicetre
France

Acta Obstet Gynecol Scand 57 349–353 1978

FRACTURE AND CHEMICAL COMPOSITON OF THE DEPOSIT FORMED ON THE LIPPES LOOP AFTER PROLONGED USE

Y Biale S Lazer and N Ben Aderet

From the Department of Obstetrics and Gynecology A Soroka Medical Center and Faculty of Medicine Ben Gurion University Beersheba Israel

act In order to confirm or refute the theory that is the need to replace IUD s every few years due to ing 76 Lippes Loops were tested The sedi found on the devices was composed mainly of im carbonate After removal of the sedimentation it seen that there was some corrosion of the body of the es which caused a decrease in the IUD thickness ture tests showed that an IUD which has been in use long period of time is more rigid has less ability to m and breaks under less pressure It seems that the nt medical opinion stating that IUD s should be re d every few years is valid

many advantages of the intrauterine contracep d vice (IUD) are the reasons for the spread of se and its importance as a method of birth rol In its present varied forms it is normally e from plastic which occasionally breaks when evice is in position This breakage can result in minal pain bleeding and difficulty in removal) As a result of these hazards medical au es concerned with family planning feel that is a need to routinely replace an IUD every years (3 4)

order to confirm this theory 26 IUD s of the es Loop type have been tested These were in uterus for various periods of time up to a maxi n of seven years

he variables used for these tests were

The composition of the sediment deposited on devices

Deformation of changes in thickness due to the gth of time in use

The amount of pressure required to break the ces

METHODS AND RESULTS

Lippes Loops Size C which remained in the uterine ty for up to seven years were tested Nine of the Ys were broken within the uterine cavity Removal of IUD's was performed either because of expulsion of a piece of loop without symptoms or because of pain or irregular uterine bleeding In the former group there were four women and in in the latter 2? women Amongst the group of ?2 women 5 were found to have broken IUD s and in 2 IUD threads could not be seen but X rays revealed the broken IUD s In three cases the diagnosis of broken IUD was made during its removal We do not think that the attempted removal caused the break age since the IUD s were broken several times In one case a woman was pregnant with a broken IUD

Immediately after removal the loops were washed with ion free distilled water to free them from any adherent matter and then thoroughly air-dried The solid incrustations formed on the Lippes Loops were extracted with dilute hydrochlorid acid

The devices were weighed before placing the IUD in hydrochloric acid and afterwards thus the amount of the sediment was quantified The CO_2 produced by the action of hydrochloric acid and the sediment was absorbed in a solution of calcium hydroxide and measured by titration

The sediment upon several IUD s was scraped weighed and burned into ash with oxygen added and the CO produced was measured This represents the total carbon of the sediment The total carbon consists of an organic carbon fraction and an inorganic fraction that is carbonate The organic carbon fraction is determined by subtracting the CO_2 produced by the sediment in hydrochloric acid from the total CO_2 measured by burning the sediment The amount of the various cations in the hydrochloric acid solution was estimated by atomic absorption Perkin Elmers spectrophotometer model 303

Table I *Composition of the Deposit as related to duration of I U D in utero (percentaage of total weight)*

No traces of aluminium cobalt copper manganese and iron

Duration in uterus (years)	Number of devices	Calcium car bonate	Mag nesium	So-dium	Zinc
0 5	3	80 2	0 39	1 7	0 14
1	3	81 8	0 41	1 87	0 15
2	10	83 1	0 32	1 8	0 19
5	8	77 2	0 32	0	0 21
7	2	78 5	0 35	1 83	0 18

Table II *Comparison of identical segments of broken and unbroken IUD s (thickness in millimeters)*

Numbers of IUD s tested are given within parentheses

Order of Segment	New (3)	Unbroken 2 years (2)	Unbroken 5 years (7)	Broken 2 years (7)	Broken 5 years (3)
I	1 89	1 86	1 85	1 78	1 79
II	1 57	1 59	1 57	1 44	1 42
III	1 82	1 83	1 80	1 80	1 78
IV	1 57	1 57	1 52	1 42	1 39
V	1 83	1 82	1 80	1 75	1 73
VI	1 53	1 52	1 53	1 39	1 36
VII	1 72	1 73	1 70	1 67	1 69
VIII	1 44	1 43	1 43	1 40	1 38
IX	1 65	1 64	1 62	1 58	1 58

depression whereas a device which had been in use for 5 5 years would break when a pressure of 25 kg was applied (Fig 3) The graphical presentation of such an experiment is given in Fig 4

DISCUSSION

The modern plastic IUD has been in use since the early 1960 s and since then many side effects have been described such as abdominal pain irregular uterine bleeding pregnancies and expulsion of the device The present paper reports on uncommon complication which has received little attention that is the fracture of the device *in situ*

Fractures of plastic IUD s appear after retention in the uterine cavity for at least two years (1 2 4) Fragmentation occurs in 1–3% of insertions (1 2) and the clinical manifestation is generally expulsion of a piece of loop without symptoms Less frequently pain or irregular uterine bleeding occur necessitating hospitalization and anesthesia for removal of the IUD fragments Fracture may affect the contraceptive action and an increased rate of pregnancies is abbributed to broken IUD s (1 5) A pregnancy associated with a broken IUD was observed also by us Because of the above mentioned complications it is recommended to remove the fragmented loops (1) and some authors have adopted the practice of removing loops after two or more years and inserting fresh loops (3 4)

The use of Lippes Loop is very popular and since relatively more information about its fragmentation is available (2 4 6) we decided to estimate the structural changes and the composition of the deposit on a Lippes Loop After retention in the uterus for some time IUD s develop a rough pitted surface due to depositions of calcium salts and the extent of the deposit appeared to be related to the time the IUD had been retained (6 7 8) Engineer et al (8) had observed that the various constituents including protein accounted for about 70% of the total solid incrustation present on a device and that the chemical nature of the remaining 30% of the material could not be elucidated We found that the inorganic portion is greater composed mainly of calcium carbonate (around 80%) and about 20% is organic material Also the magnesium level was found by us to be much lower i e 0 3% when compared with the 10% found in their work We demonstrated the presence of 2% sodium and 0 15% zinc while Engineer et al (8) did not find these cations Neither Engineer et al nor we could demonstrate traces of cobalt or copper It is interesting to note that Kar et al (9) reported that calcium was slightly increased and bicarbonate slightly decreased in the intrauterine fluid of IUD fitted patients The rough solid deposit on the IUD is not responsible for bleeding by an abrasive action on the endometrium (7)

Another interesting observation is the erosion of the body of the devices with the appearance of moth eaten cloth The extent of the corrosion increased in proportion to the length of time that the device had been used The corrosion caused a decrease in the IUD thickness in those devices which had been broken These changes may be related to the chronic foreign body reaction by the endometrium to the presence of an IUD It has been shown that polymorphonuclear leukocytes and mononuclear cells are present more frequently and in increased numbers in uterine flushings of animals with IUD s The total protein reducing sugar and hemoglobinase values are also higher (10 11 12)

Our findings comfirm the observation made by others (4 6) that the length of time in use causes an increase in rigidity and decrease in flexibility of the devices As a result the longer a device is in the uterine cavity the less susceptible it becomes to deform and breaks under less pressure Naturally the IUD tends to break at the curved areas This is evidently due to fatigue caused by deformation under uterine contraction In addition the tests showed that the structural thickness decreased when the devices were in use for a long time

It is clear that comprehensive results and deductions can only be obtained by expanding the s…

s and the amount of testing Nevertheless it been demonstrated that the current medical on stating that IUD should be replaced every ears is a valid theory

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Submitted for publication July 1 1977

Y Biale
Department of Obstetrics and Gynecology A
Soroka Medical Center
Beersheba
Israel

Acta Obstet Gynecol Scand 57 355–359 1978

INFLUENCE OF PUBOCOCCYGEAL REPAIR ON URETHRAL CLOSURE PRESSURE AT STRESS

Gorel Bunne and Anders Obrink

From the Department of Obstetrics and Gynecology Karolinska Institutet Sabbatsberg Hospital Stockholm Sweden

...act Stress incontinence is cured or improved by ...al treatment but the immediate reason is obscure ...taneous urethrocystometry with urethral pressure ...e recording at rest pre and postoperatively has ...n that the urethral pressure remains fairly unchanged ...e operation Similar measurements but during ... have been performed in eight women with stress ...tinence before and after pubococcygeal repair with ...st focussed on changes in pressure transmission ...abdomen to urethra We have found that the reason ...ure is a greatly improved pressure transmission ...ibly depending on the firm support beneath the ...ra postoperatively Rotational descent is prevented ...he floor" beneath the urethra responds with good ...terpressure at stress The pressure transmission was ...od at one year as at one month after surgery pointing ...asting result

...ococcygeal repair a well known and much used ...ation for stress incontinence was introduced ...Ingelman Sundberg in 1947 (3) Several re...spective studies have shown that it is suitable for ...ng severe degrees of stress incontinence (4 6) ...sures at rest in the urethra and in the blad... before during and after the operation have ... investigated by means of simultaneous ...hrocystometry (7) The only postoperative ...nge in the urethral pressure profile (=the in...minal pressure recorded continuously through the entire length of the urethra) was a broader ... of maximal pressure in place of the distally ...ted point of maximal pressure found to be typi... of stress incontinence This alone cannot ...ount for the transformation from stress inconti...ce to continence although it might be of margi... importance

...e have found that the main determinant of the ...ree of continence or stress incontinence is the ...gnitude of the urethral closure pressure at rest ...ecting the tone of the smooth and striated mus...s in the urethral wall and in its surroundings ...luding the supporting tissues (2)

Pubococcygeal repair did not make any contribution to the maximal urethral pressure There was on the contrary a tendency to a lowered pressure possibly reflecting damage to the urethral blood supply in connection with the vaginal dissection (7) Thus the reason for cure could not be concluded from measurements at rest Most likely improvement arose from a better transmission of pressure from abdomen to urethra To verify this eight patients were examined both pre and postoperatively in a dynamic situation simulating the efforts of daily life by coughs of different strength The equipment used for simultaneous urethrocystometry was elaborated in 1974 (1) and gives a good precision and reproducibility even at high frequencies and amplitudes Dynamic studies are made feasible by the use of a thin semiflexible catheter containing the pressure measuring areas Accordingly the results of the operation can be evaluated not only from the patient s history but also objectively by determining the exact margin to leakage at different degrees of straining Among other things pressure transmission from abdomen to urethra can be calculated To further evaluate any improvement in this respect six women have been examined in the same manner one year post operatively

MATERIAL AND METHOD

Eight women mean age 57 years (r=69–43) mean parity 0 (r=3–1) with genuine stress incontinence of second degree on the Ingelman Sundberg scale (5) were examined pre and one month postoperatively No patient had been operated on previously and all had a marked downward rotation of the anterior vaginal wall including the bladder neck area at straining A Bonney positive urinary leakage could be provoked All were similarly treated surgically with pubococcygeal repair as described by Ingelman Sundberg This involves an arcuate incision at introitus dissection of the anterior vaginal wall sutur

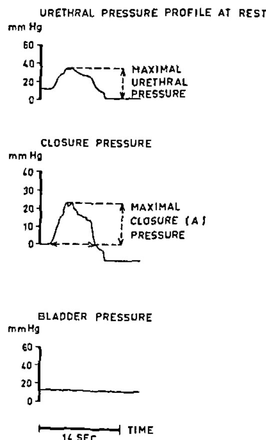


Fig 1 The three simultaneously recorded parameters

ing the pelvic fascia in the midline to elevate the bla and bladder neck cutting the pubococcygeal m bilaterally and using the anterior portions for a m sling to support the proximal urethra The distal ureth supported by *part of the two bulbocavernous* m sutured together in midline

The equipment used for simultaneous ure cystometry consists of a thin (diam 3 mm) flexible Dacron catheter with two sensor areas, o its tip and another 60 mm proximally three amplifier a recorder Electronic subtraction gives the closure sure (=urethral pressure minus bladder pressure) T cord the urethral pressure profile the catheter was d by a motor through the urethra at a velocity of

In the lithotomy position the urethral pressure p rest was recorder at bladder volumes of 100 and 300 each volume cough profiles during light (appr mmHg) moderate (approx 30 mmHg) and s (approx 50 mmHg) coughs were also recorded Th tients coughed repeatedly approximately once a se with constant force while the profile was registered the urethral wall comes into direct contact with th s areas (as when the urethra is kinked or extremely nar artefacts may render interpretation of the profile s what *difficult Consequently* these measurements supplemented with another estimation of the degr pressure transmission This was obtained by h ld catheter manually with the proximal sensor area a point of highest urethral pressure while the p coughed repeatedly as described above

Six women mean age 54 years (r=69–43) mean p 2 5 (4–1) were examined in the same way one year

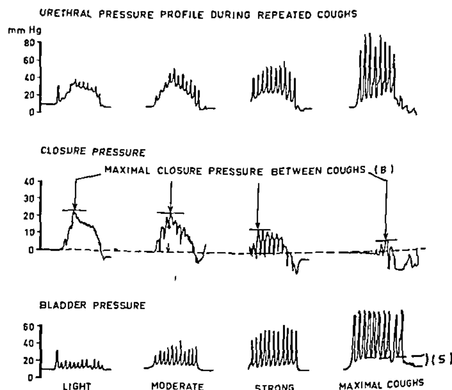


Fig 2 The same parameters as in Fig 1 during repeated coughs

occygeal repair For this investigation only the de
of *pressure transmission was calculated*

FINITIONS AND INTERPRETATIONS

ure The pressure within the urethra in rela
o the atmospheric pressure
vesical pressure The pressure within the bladder
ation to the atmospheric pressure
thral pressure profile Continuous recording of the
uminal pressure throughout the entire length of the
ra
thral closure pressure The intraurethral pressure
s the bladder pressure (At rest=A)
functional length of the urethra The part of the
ra were the intraluminal pressure exceeds the blad
ressure
urethral maximal closure pressure between repeated
hs.
dynamic urethral maximal closure pressure (at the
ent of a cough)
B signifies the loss of urethral closure pressure im
ately after repeated coughs This reduction can be
ined in part by a defective transmission of abdominal
is during the recording of the urethral cough profile
tly by a loss of urethral pressure which will be
ssed below
e the degree of straining (mmHg) calculated from the
der pressure curve at the time of maximal dynamic
re pressure
C signifies the defect in pressure transmission to
ra at a cough (The bladder pressure can be supposed
ect the intra abdominal pressure)
C the total loss of urethral closure pressure at the
ent of cough
(B+S) signifies the minimal loss of urethral closure
ure that is not attributable to defective transmission
ain between coughs
Figs 1 and 2

RESULTS

patients were subjectively cured by the opera
The bladder neck was well elevated no
ficant rotational descent occurred at straining
the muscle sling had contractile ability No
ary retention was seen postoperatively except
e case (residual *volume of 150 ml)*
s seen from table I the functional length and
bladder pressure remained unchanged after
ery while the max*imal urethral pressure*
ned slightly deteriorated
he obvious improvement in pressure transmis
is shown in table II (see B–C) Four fifths of
intraabdominal pressure increase were trans
ted to the urethra postoperatively diminishing
and thus increasing C the margin to leakage

Table I *Values at rest*

n=8 The data are mean values with the standard deviation in parenthesis

Bladder content ml	Before surgery 100	Before surgery 300	After surgery 100	After surgery 300
Functional length (mm)	25 4 (4 21)	4 3 (5 60)	25 6 (3 96)	25 8 (3 54)
Max closure pressure (mmHg)	*22 1* (2 85)	*21 4* (3 16)	17 3 (6 65)	*15.3* (4 40)
Bladder pressure (mmHg)	*10 3* (3 54)	*10 9* (2 80)	*9 8* (2 96)	*9 9* (1 89)

Student s *t* test has been used for the statistical analysi *Statistically significant differences before and alter operation* are italicized ($p<0.05$)

*However C was not as great as expected consider*ing the constantly improved pressure transmission This is explained by the slight reduction in closure *pressure at rest which was brought about by the* operation

DISCUSSION

No divergences in the pressures at rest were seen compared with previous investigations of the results of pubococcygeal repair (7) The short functional length typical of stress incontinence persisted The tendency to a lowered urethral closure pressure noticed earlier was verified Obviously the impaired vascularization after extensive vaginal dissection causes a reduction in urethral pressure by influencing the tone of the urethral smooth and striated muscles If the initial preoperative urethral maximal pressure is very low it is especially important to avoid *further reduction and* hesitation about the benefit of a vaginal operation is justified On the other hand it was clear that this *reduction in urethral pressure could be made up for* by the greatly improved pressure transmission of the urethra accomplished by pubococcygeal repair

Both in continence and in stress incontinence the loss of pressure on the way from abdomen to urethra amounts to 35–40% of the pressure increase in question (2) this may be compared with approximately 20% after pubococcygeal repair A much better transmission than ever seen in middle aged continent women had been accomplished Of the intra abdominal pressure increase at any effort 80% reached the most effective part of the functional urethra this was enough to maintain conti

Table II *Values during coughing (mmHg)*
The data are mean values with the standard deviation in parenthesis

Bladder content ml	Before surgery 100	Before surgery 300	After surgery 100	After surgery 300
Light coughs (approx 15 mmHg)				
A	22 1	21 4	17 3	15 3
B	19 8 (4 71)	17 3 (4 74)	16 3 (6 52)	13 4 (4 81)
C	16 5 (4 57)	13 9 (5 03)	12 9 (6 4?)	10 5 (5 48)
B–C	3 ? (0 46)	3 4 (0 74)	3 4 (1 30)	2 9 (0 99)
A–(B+S)	0	1 5 (2 89)	0	0
A–C	5 6	7 5	4 4	4 8
Moderate coughs (approx 30 mmHg)				
A	22 1	21 4	17 3	15 3
B	16 6 (4 24)	14 5 (5 76)	14 6 (7 29)	13 1 (5 51)
	3 6 (5 50)	3 4 (5 76)	8 5 (7 63)	7 6 (6 14)
B–C	13 0 (3 83)	10 9 (2 42)	6 1 (1 46)	5 5 (0 76)
A–(B+S)	3 4 (4 17)	3 0 (6 05)	0 1 (? 85)	0
A–C	18 5	18 0	8 8	7 7
Strong coughs (approx 50 mmHg)				
A	22 1	21 4	17 3	15 3
B	14 9 (3 67)	10 7 (4 63)	12 8 (5 85)	10 5 (5 04)
C	–2 1 (3 53)	–8 1 (4 34)	3 5 (5 93)	2 4 (5 34)
B–C	18 4 (3 95)	19 0 (3 27)	10 5 (4 38)	8 ? (1 96)
A–(B+S)	5 0 (6 2?)	7 7±0 (5 ?5)	1 6 (1 9?)	? 5 (2 97)
A–C	24 2	29 5	13 8	12 9

Student s *t* test has been used for the statistical analysis Statistically significant differences before and after operation are italicized ($p<0.05$)

nence even with strong coughs in spite of the low maximal closure pressure at rest

The sutured pelvic fascia and above all the muscle sling create a firm floor under the urethra keeping it in a normal or slightly elevated position even during intense straining Downward rotation is prevented almost entirely The counterpressure exerted by this floor is certainly much better than

Table III *Transmission after 1 year (mmHg)* $n=6$

Bladder content ml	100	300
B–C light coughs	?0 (0)	23 (0 ?1)
B–C moderate coughs	6 3 (? 50)	63 (1 6?)
B–C strong coughs	8 8 (? 49)	95 (3 2?)

that produced by a sagging anterior vaginal wall We b~l eve that the support for the urethra is more important than elevation in itself although technically elevation is a condition for achieving a g a support Bonney s test for example elevates the urethra but also prevents downward rotation at straining by support from the examiner s fingers or an instrument As soon as rotational descent is allowed leakage appears in stress incontinence

One year postoperatively pressure transmission was found to be equally good indicating that no relaxation or destruction of the urethral support had occurred In a follow up (6) the major recurrences after pubococcygeal repair occurred during the first postoperative year often before healing was complete Most likely they are due to rupture of the muscle sling deprived of its solid floor the urethra yields to a sudden strain and pressure transmission is again as defective as in stress incontinence If the muscle sling is still effective after one year the long term prognosis should be good

CONCLUSION

Pubococcygeal repair ad modum Ingelman Sa berg cures stress incontinence by furnishing the urethra with a solid floor thereby preventing rotation al descent at straining and resulting in a e ed improved transmission of pressure from abdomen to urethra Losses are reduced to approximately ?? which converts stress incontinence into continence The improvement is maintained during the first postoperative year (=the observation time) probably much longer

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Submitted for publication May 19 1977

Gorel Bunne
Department of Obstetrics and Gynecology
Sabbatsberg Hospital
Stockholm
Sweden

Acta Obstet Gynecol Scand 57 361–365 1978

CRYOSURGICAL TREATMENT OF DYSPLASIA AND CARCINOMA IN SITU OF THE CERVIX UTERI

Yngve Einerth

From the Department of Obstetrics and Gynaecology, Helsingborg Hospital, Helsingborg, Sweden

act Fifty nine patients (age range 18–40 years mean ars) with dysplasia or carcinoma in situ of the cervix were treated with cryosurgery Healing occurred in tients (91 6%) after one treatment (double freeze ic) and in ? patients after refreezing No early or late ications occurred during a follow up period of 7–37 hs Five of the patients with carcinoma in situ were ved *immunologically* with determinations of serum (tissue polypeptide antigen) which can be employed arameter of malignancy In all instances the initially ted TPA normalized after cryosurgical treatment surgery is a simple painless and safe treatment od in ectocervically localized carcinoma in situ and asia that is particularly suited for out patient use

routine use of vaginal cytology has resulted in increased number of diagnosed cases of noma in situ In 1970 the number of diagnosed s of in situ cervial cancer in Sweden was ac ing to the official Swedish Cancer Register tly more than 4000 (26) The predominant ment of carcinoma in situ is surgical conization 17 18) In more recent years however the ber of conizations performed has *decreased* what owing to the introduction of alternative radical methods as e g ring biopsy (20) Con on gives a healing frequency in excess of 95% but necessitates hospitalization and is attend h various complications viz post operative norrhage varying in frequency between 6 6 and in different studies (8 10 15 16) cervical osis in 4 to 6 6% (10 15 17) and also probably main increase in the frequency of spontaneous rion premature delivery and complications ng childbirth although there are some con ictions in the published works (10 17) uring the last decade cryosurgery has been iched as an alternative to surgical conization of malignant conditions of the uterine cervix (5 6 22 23 24 25) The indication for *cryosurgery* been limited to discrete colposcopically visible lesions on the ectocervix as the diagnosis and cryosurgical management of endocervical lesions has been found to be unsatisfactory (5 24 25)

The healing rate after cryosurgery varies between 81 and 97% There are few complications a few cases of salpingitis have been reported but there have not been any confirmed occurrences of cervical stenosis or any untoward effects with respect to fertility or pregnancy (5 14 22 23 24 25)

Besides the immediate tissue necrotizing effect of the cryosurgical procedure there is also some evidence for a late induced immunological effect There is a rise in the titre of different tumour antibodies after cryosurgery (12 21)

In these investigations there was a greater increase in titre than after conventional surgery or radiotherapy and even greater than the antibody response that is obtained after the injection of tumour extract

MATERIAL AND METHODS

Women were selected who had had two ro three vaginal smears (VS) showing abnormal cells consistent with dysplasia or carcinoma in situ Cervical curettage and a colposcopically selected biopsy of the portio vaginalis were performed The colposcopic evaluation of the cervix showed in most cases areas of white epithelium and abnormal vascular pattern referred to as mosaic or punctuation (5 11) and was used for identifying areas to be biopsied No treatment was given and after 3 months further cytological smears were taken This was done because of colposcopically selected biopsies have been proved to be curative in up to 50% of cases (1)

Three patients with endocervically localized lesions and 1 patient with micro-invasive cancer were identified and given other forms of treatment In 39 patients the biopsy was curative Thus 59 patients remained who had persisting dysplasia or carcinoma in situ these women were given cryosurgical treatment (Fig 1)

Freezing was performed with the MT 500 Multitip Gyn Cryosurgical Probe manufactured by Cryomedics Inc Bridgeport Connecticut USA Applicators of differ

without anaesthesia moreover as a rule there is no post operative incapacity

In the present investigation the agent employed was carbon dioxide which gives a temperature of about −70 C In other investigations as well as carbon dioxide nitrous oxide and freon have been used which provide a temperature of about −90 C as well as liquid nitrogen which yields a temperature of −190 C No controlled clinical study has been published to date in which the effects of different refrigerant agents have been compared It is *very likely that* the treatment period can be *shortened and perhaps the procedure can be simplified by using gases yielding a lower temperature but the most important prerequisite is that the rate of temperature fall exceeds 5°C per sec this is* obtained even with carbon *dioxide (12) Freezing in two sessions with a short thawing period in between has also proved to give better results than a single* session (5 9)

The results of the present investigation accord with earlier published studies (5 14 22 23 24 25) in the *absence of early* and *late* complications The present results do not suggest that a previously contracted salpingitis or an in situ intra uterine device should constitute a contra indication

It is considered important to perform the cryosurgery in the early proliferative phase of the uterine cycle because the appreciable cervical oedema that the treatment engenders during the first post operative week might cause temporary cervical obstruction and consequently a risk of haematometra There have not been however any observed untoward effects as regards fertility or pregnancy nor have there been any confirmed occurrences of cervical stenosis These findings make the method a suitable one especially for women that desire to have further children

A careful follow up like that conducted after surgical conization is essential Refreezing can be performed in cases of *persistent* dysplasia and the *possibility always* remains open for surgical conization *There have not been any recurrences of dys*plasia or carcinoma in situ in this *study but the* observation period is still *rather short* Crisp (6) has however followed 60 patients cryosurgically treated for severe dysplasia for 6–7 years and has not found any recurrences

In 1957 Bjorklund et al (2) discovered and purified a polypeptide with antigenic properties tissue polypeptide antigen (TPA) This antigen occurs in tumour tissue and pathologically elevated TPA activity *in the serum* can be demonstrated in some *patients with a malignant desease (3 7 19* There is a correlation between remission in the treatment of malignant tumours and the return to normal of the TPA activity as well as between rising TPA activity and progressive tumour disease (4) In 5 patients with carcinoma in situ in the present investigation that initially had a slightly pathologically elevated TPA activity in the serum levels fall to normal after cryosurgical treatment all 5 patients were also colposcopically cytologically and histologically completely healed TPA activity may be a useful index of successful treatment

CONCLUSIONS

Cryosurgery is a rapid non *anaesthesia requiring method of* treatment that can be used in dysplasia and carcinoma in situ localized and limited to the ectocervix It is above all suitable for younger age groups The method places high demands on a correct pre operative diagnosis The treatment can be *performed on an out patient* basis and there is as a *rule no post* operative incapacity There has been complete remission in more than 90% of the patients that were treated The method is not accompanied by any early or late complication nor does it appear in any way to adversely affect fertility or pregnancy

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Submitted for publication April 22 1977

Yngve Einerth
Lakargruppen
Sodergatan 39
S 252 25 Helsingborg
Sweden

Acta Obstet Gynecol Scand 57 367–369 1978

SHORT COMMUNICATIONS

HUMAN PLACENTAL LACTOGEN LEVELS IN AMNIOTIC FLUID IN NORMAL AND TOXEMIC PREGNANCIES

D Lolis and D Kaskarelis

From the First Department of Obstetrics and Gynecology University of Athens Alexandra Maternity Hospital Greece

Abstract Amniotic fluid human placental lactogen (HPL) levels were measured by radioimmunoassay in 162 cases of women with normal pregnancy and 43 with toxemic pregnancy in the last trimester of pregnancy A significant difference in levels was observed

Previous investigations have measured human placental lactogen levels in the amniotic fluid in only a few cases of both normal pregnancies and pregnancies complicated by Rhesus isoimmunization However nothing has been reported for measurements of HPL in amniotic fluid in toxemic pregnancies (7 8 9 14 23)

The present study was to investigate the value of fluctuations of HPL levels in amniotic fluid at various weeks of normal and toxemic pregnancies in order to evaluate the fetal distress

MATERIAL AND METHOD

A total of 205 amniotic fluid samples were collected from 162 women with normal pregnancy and from 43 women with toxemic pregnancy between the 28th and 42nd week of gestation These cases were classified into four groups according to the age of gestation as follows

Group A 28th to 33rd week 33 cases
Group B 34th to 36th week 31 cases
Group C 37th to 39th week 55 cases
Group D 40th to 42nd week 86 cases

The amniotic fluid samples were taken by amniocentesis when the cervical dilatation was no more than 5 cm

All the samples were put in plastic tubes with code Nos and sent to the laboratory where the origin of sample (i e from normal or toxemic pregnancy) was unknown

They were then centrifuged and the serum stored at −20°C until complation of the calculation of hormone by radioimmunoassay In the present study the Amersham HPL kit was used for determination of HPL level in amniotic fluid

RESULTS

The results of investigation are presented in Table I A significant difference of HPL values was observed between normal and toxemic pregnancies even though it was observed that the values rose both in normal and toxemic pregnancies until the 34th–36th week Thereafter there was a decline (Fig 1)

DISCUSSION

In recent years the study of the hormones and enzymes of amniotic fluid have been started It can be supported that the determination of amniotic fluid s hormones is useful for the estimation of the endocrinic status of the fetus (15)

Many investigations have been published about HPL levels in the maternal blood in normal and abnormal pregnancies as a means of observing the condition of the fetus but there are limited in

Table I Mean values of the amniotic fluid HPL (μg/ml) in normal and toxemic pregnancies

Age groups in gestational weeks	Normal pregnancies				Toxemic pregnancies				
	n	*X*	S D	S E	*n*	*X*	S D	S E	*t*
A 28–33	18	0 78	0 430	0 100	15	0 50	0 0[illegible]0	0 004	2 800
B 34–36	19	0 85	0 356	0 081	17	0 59	0 0[illegible] 0	0 050	3 [illegible]09
C 37–39	45	0 7[illegible]	0 400	0 050	10	0 41	0 238	0 075	3 563
D 40–42	80	0 64	0 0[illegible]2	0 002	6	0 17	0 148	0 060	7 833

$P<0\ 01$ $P<0\ 001$

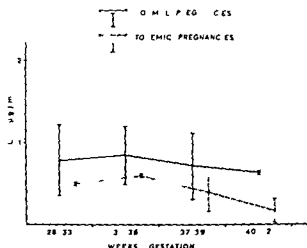


Fig 1 Mean values and standard deviations of amniotic fluid HPL in normal and toxemic pregnancies

vestigations about the fluctuations of HPL in amniotic fluid (2 5 8 9 12 14 16 17 19 23)

In this study determinations of HPL levels were made in amniotic fluid in a large number of normal and toxemic pregnancies The amniotic fluid samples were taken at the beginning of labour in order to avoid the influence of labour in HPL levels (8) It was found that the HPL levels rose reaching the highest value between the 34–36 week of pregnancy Thereafter there was a decline Our findings that the HPL levels rose with progress of pregnancy agree with findings of other investigators but there are different opinions as to which week of pregnancy the HPL levels stop rising (1 3 6 7 10 11 18 20 21 22)

It was noticed that the HPL levels of amniotic fluid of toxemic pregnancies are much lower than in normal pregnancies at the same week It is not possible to compare our findings with others because this has never been done before by other investigators

How the HPL is carried from the blood circulation into the amniotic fluid is unexplained (4) According to the opinion of Josimovich et al (10) the HPL passes through the placenta into amniotic fluid from the membranes by diffusion but it is necessary to carry out further investigations in order to fully explain this problem (13)

In conclusion the present study showed that measurement of HPL of the amniotic fluid is a good parameter for the estimation of fetal risk in cases with toxemia Even one sample may help in the diagnosis of impending fetal distress or be an indication of fetal death

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Submitted for publication Dec 16 1976

D Lolis
First Department of Obstetrics and Gynecology
University of Athens
Alexandra Maternity Hospital
80 Vass Sophias and K Lourou Str
Athens (611)
Greece

CASE REPORTS

PREGNANCY IN A CASE OF NELSON S SYNDROME

Sara Leiba Haiuta Kaufman Gideon Winkelsberg and Charles M Bahary

From the Department of Endocrinology the Department of Obstetrics and Gynecology and the Endocrine Laboratory Beilinson Medical Center Tel Aviv University Medical School Petah Tikva Israel

Abstract A woman suffering from Cushing s disease from the age of 17 who had been treated consecutively with pituitary irradiation bilateral partial adrenalectomy and o p DDD (Mitotane USP) presented the clinical picture of Nelson s syndrome (hypoadrenalism with secondary hypersecretion of ACTH and MSH) at the age of 37 Under substitution therapy with corticoids she became pregnant for the first time at the age of 38 The course of the pregnancy was normal and at term she was delivered of a normal child by Cesarean section The materno fetal relationship the increased risk of pituitary infarction during pregnancy and the possible teratogenic effect of chemotherapy in such cases are discussed

In most cases of Cushing s syndrome that have undergone chemical or surgical adrenalectomy there is *permanent* hypersecretion of ACTH and MSH In a considerable number of these cases the long standing hypersecretion is associated with hyperplasia of the pituitary gland adenoma formation and secondary enlargement of the sella turcica (Nelson s syndrome) A woman who becomes pregnant under such conditions poses a number of problems in relation both to herself and her child

We recently had under our care a patient in whom Nelson s syndrome appeared at the age of 32 following treatment for Cushing s disease by bilateral partial adrenalectomy and pituitary irradiation as well as by o p DDD (Mitotane USP) She became pregnant at the age of 38 The following is the case report of this patient

CASE REPORT

L B had suffered from Cushing s syndrome from the age of 17 years She was given irradiation to the pituitary to a total dose of 30 000 r over a period of 6 years At the age of 27 symptoms recurred and she underwent bilateral partial adrenalectomy Three years later there was another recurrence and chemotherapy was instituted with o p DDD at a dose of 5 g daily for a total dose of 500 g At the age of 37 the patient presented with hypoadrenalism and required substitution therapy with corticoids Periodic examination of the sella turcica visual fields and routine analyses were normal with the exception of the low levels of adrenal steroids and the high level of blood ACTH (350 pg $^{-1}$) (Table I)

The patient s menarche occurred at the age of 13 and she menstruated normally until the first symptoms of Cushing s disease developed She was amenorrhoic throughout the period of excessive adrenal activity but began to menstruate again once the level of blood corticoids had returned to normal Beginning in 1968 under substitution therapy with corticoid her menstrual cycles were relatively normal

In 1975 the patient became pregnant and was very anxious to have the baby It was decided to allow her to continue the pregnancy taking particular care to carry out visual field and gynecological examinations as well as endocrine tests at frequent intervals There was a moderate increase in the levels of urinary 17 OHCS 11 OHCS and estriol and in the levels of blood 11 OHCS but a sharp rise in plasma ACTH levels the maximum being found one week before delivery (Table I) The patient became more pigmented but had no headaches and the visual fields remained normal

In the 36th week of gestation the patient appeared with regular uterine contractions and a Cesarean section was performed Two hours prior to operation and during the operation she received 700 mg hydrocortisone which was gradually reduced following delivery The infant a female weighing 600 g was found to be in good health and was not pigmented The post-operative course was uneventful

DISCUSSION

This case of hypoadrenalism and secondary hypersecretion of ACTH had undergone treatment with both irradiation to the pituitary and a cytostatic drug Her relatively advanced age when there is a greater likelihood of chromosomal aberration also contributed to the factor of risk Pregnancy under these conditions raises a number of questions worthy of consideration 1) the function of the fetal pituitary axis when the mother is receiving substitution therapy with corticoids and has a permanent hypersecretion of ACTH 2) the increase danger of infarction of a hyperfunctioning pituitary gland dur

Received 1977

Table I

	Urinary						Blood						
Date	Vol	17KS	17OHCS	11OHCS	*Total estrogens*	Estriol	ACTH	*11OHCS*	Estradiol	*Progesterone*	Testosterone	*Aldosterone*	Observations
1973													*Treatment*
30 XI	450	2 5	6 1										hydrocortisone ?0 mg/day
1975													
1 III							350						
9 III							315						
9 XI	600	1 2	5 8	33	16		400	6 4	600	23	25	7	Last
24 XI	1 150	1 9	6 6		65 5			6 9					menstruation
23 XII	500	2 2	4 7	76	267	? 4	800	4 6		35	?8 7	4 5	20 VIII 75
1976													*Treatment*
1 II	600	1 3	5			5	>1 500					8	meticorten
23 III	560	2 8	5 7			6 4		9 4					5–7 5 mg/day
6 IV						10 7							fluorinef
28 IV	700	3 2	7 4	196		17 7		13 4					0 1–0 ? mg/day
15 V						16 5							Cesarean
18 V							>2 160	11 ?					section
													25 V 75
10 XI	700	2	2 8				1 000	1 8					*Treatment* meticorten
7 XII	600	3 2	4 1	22 6			600	2 9					5–7 5 mg/d y fluorinef 0 1–0 ? mg/day

Normal levels

Urinary
- 17KS 8–14 mg/24 h
- 17OHCS 4–16 mg/24 h
- 11OHCS 50–150 µg/24 h

Total estrogens
- 15–35 µg (midcycle peak)

Estriol in pregnancy
- 16 weeks 2 mg/24 h
- 20 weeks 5–8 mg/24 h
- 27 weeks 10 mg/24 h

Blood
- ACTH 30–80 pg/ml (RIA—a kit supplied by Radiochemical Ltd Amersham Engla
- 11O HCS 11–23 µg/24 h
- 17 beta estradiol (in pregnancy) 250 pg (greater than midcycle peak)
- Progesterone (in pregnancy) 17 mg/ml (greater than luteal phase level)
- Testosterone 20–60 ng/100 ml
- Aldosterone 5–16 ng/100 ml

ing pregnancy 3) the possible cytotoxic and teratogenic effect of the o p DDD even though it was administered a number of years before the pregnancy

1) The literature contains data (2 4 6 9) indicating that pregnancy may compensate maternal cortical adrenal insufficiency through transfer to the mother of part of the corticoids secreted by the fetal adrenals glucocorticoids are able to cross the placental barrier in both directions influencing the function of both the maternal and fetal pituitary adrenal axis ACTH in contrast cannot cross this barrier (1 5 7 10) and the maternal ACTH level has no influence on the fetal pituitary adrenal function It is concluded that hypersecretion of ACTH should not be considered a contraindication for pregnancy

2) It is known that the pituitary gland enlar appreciably during normal pregnancy and regres rapidly but incompletely after delivery There ha been several reports of rapid tumor growth dur pregnancy requiring emergency treatment (3) F this reason some clinicians recommend irradiat of the pituitary prior to the administration of fer ity drugs in patients presenting with infertility a pituitary enlargement

In our patient the sella turcica was not enlarg but there was evidence that the pituitary w hyperactive despite the considerable dose of radiation she had received in the past the level ACTH which was significantly elevated at the b ginning of pregnancy subsequently rose conside bly until the last month before delivery Fortuna ly the patient felt well had no headaches and l

sual fields remained normal throughout the pregnancy and after delivery

3) o p DDD is a cytotoxic drug specific for adrenal cells Since the adrenals and gonads are of the same embryological origin it is possible that this drug might have a teratogenic effect on the gonadal cells thus affecting future offspring Luton et al (8) reported two patients who gave birth to normal infants after having received o p DDD one patient conceived 6 months after discontinuation of the drug and the other during therapy These cases together with ours strongly suggest that treatment with o p DDD particularly when it has been administered long before conception is not a contraindication to pregnancy

The factor which finally determined our decision to allow this patient to continue with her pregnancy was her strong desire to have a baby It must be stressed however that in all similar cases the danger of pituitary infarction remains the most important risk Thus each such case must be assessed carefully before the patient is allowed to continue a pregnancy

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Submitted for publication April 28 1977

Sara Leiba
Department of Endocrinology
Tel Aviv University Medical School
The Beilinson Medical Center
Tel Aviv
Israel

Table I

Date	Urinary Vol	17KS	17OHCS	11OHCS	Total estrogens	Estriol	Blood ACTH	11OHCS	Estradiol	Progesterone	Testosterone	Aldosterone	Observations
1973													*Treatment*
30 XI	450	2 5	6 1										hydrocortisone
1975													20 mg/day
1 III							350						
9 III							315						
9 XI	600	1 2	5 8	33	16		400	6 4	600	23	25	7	Last
24 XI	1 150	1 9	6 6		65 5			6 9					menstruation
23 XII	500	2 2	4 7	76	267	2 4	800	4 6		35	28 7	4 5	20 VIII 75
1976													*Treatment*
1 II	600	1 3	5			5	>1 500					8	meticorten
23 III	560	2 8	5 7			6 4		9 4					5–7 5 mg/day
6 IV						10 7							fluorinef
28 IV	700	3 2	7 4	196		17 7		13 4					0 1–0 2 mg/day
15 V						16 5							Cesarean
18 V							>2 160	11 2					section
													25 V 75
10 XI	700	2	2 8				1 000	1 8					*Treatment*
7 XII	600	3 2	4 1	22 6			600	2 9					meticorten
													5–7 5 mg/day
													fluorinef
													0 1–0 2 mg/day

Normal levels

Urinary
17KS 8–14 mg/24 h
17OHCS 4–16 mg/24 h
11OHCS 50–150 μg/24 h
Total estrogens
15–35 μg (midcycle peak)

Estriol in pregnancy
16 weeks 2 mg/24 h
20 weeks 5–8 mg/24 h
27 weeks 10 mg/24 h

Blood
ACTH 30–80 pg/ml (RIA—a kit supplied by Radiochemical Ltd Amersham Englar
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Acta Obstet Gynec Scand 57 377–380 1978

THE LANDRY–GUILLAIN–BARRE SYNDROME AND PREGNANCY

Greger Ahlberg and Gosta Ahlmark

From the Department of Medicine Falu Hospital Falun S eden

act The Landry–Guillain–Barre syndrome is consid ed rare in connection with pregnancy In mild cases the rse of the pregnancy is unaffected In severe cases th respiratory depression and bulbar symptoms espe ly during late pregnancy the syndrome entails an in eased risk to both mother and foetus Therapeutic abor n or cesarean section are not considered to be in ated A pregnant woman developed the disease during e final trimester and gave birth to premature twins dur respirator treatment The mother and the infants r ived

a dry (15) described in 1859 a neurological disor r with ascending paralysis which was further de ted by the specific cerebrospinal fluid (CSF) find gs of Guillain Barre & Strohl in 1916 (11) his disease—the Landry–Guillain–Barre syn ome (LGBS) or acute polyradiculitis—is a lyneuropathy of unknown aetiology The disease ects people of all ages and is somewhat more mmon in men than in women Clinically demon ble infection precedes the disease in more than of the cases (?6) and a postinfection allergic munological reaction has been suggested as the ological background Patho-anatomically there is a segmental demyelination of peripheral nerves d in severe cases perivascular inflammatory in tration of the nerve roots occurs

Typical LGBS is characterized by symmetric otor symptoms with ascending paresis which may ect both spinal and cranial nerves This paresis th impaired tendon reflexes may progress within riod of two weeks and lead to bulbar symptoms d respiratory depression Sensory symptoms in e form of paraesthesiae and muscle pain are also ually present The CSF findings are characteris with increased protein without a corresponding crease in cells—albuminocytological dissociation ight increase in mononuclear cells may occur he patient usually recovers spontaneously within months but residual symptoms occur and the ortality is not negligible

LGBS during pregnancy is rare and only a few cases have been described in the literature Most of the mothers have had the disease in relatively mild form This communication reports one of the few cases with respiratory depression in which the mother and offspring survived It is also the first twin pregnancy reported in connection with LGBS

CASE REPORT

The patient was a 8 year-old married primigravid wom an who on 5th August in the 32nd week of pregnancy developed paraesthesiae in her hand and feet without preceding infection During the following ten days she experienced progressive muscle weakness in her arms and legs and also headache On 14th August she developed right sided facial paresis and came to the hospital The course of the pregnancy had been completely normal but a twin pregnancy was suspected

The patient was mentally alert and showed signs con sistent with the 3 nd week of pregnancy The foetal sounds were normal Blood pressure was 130/80 mmHg and the ECG was normal A neurological investigation showed right sided facial paresis but the other cranial nerves were intact Incomplete paresis was present in all extremities and the patient was unable to stand up The peripheral reflexes were weak and no sensory symptoms could be detected Babinski s reflex was absent bilaterally

On 16th August further progression had occurred and the patient now had difficulty in talking and swallowing incipient double vision and also left sided facial paresis On the following day she had difficulty in controlling her micturition and was treated with catheter à demeure The pharyngoparalysis and paresis of the extremities became total and respiration deteriorated

Laboratory routine tests were normal Lumbar punc ture on 15th August showed free Queckenstedt bilaterally and clear CSF without cells and the protein concentration was 570 mg/l On 17th August the CSF protein concen tration was 640 mg/l and no cells were found The pre liminary diagnosis of the Landry–Guillain–Barre syn drome was considered confirmed

On 20th August respiratory failure occurred and res pirator treatment was started A lung X ray showed basal atelectasis on the left side Tracheotomy was performed During preparations for this procedure the water broke Labour started nine hours after the patient had been

placed in the respirator Delivery was achieved by suction Both infants who were monozygotic boys had Apgar scores of 1 but their status became normal within six hours

The mother s condition was unchanged post partum but she was treated with penicillin because aspiration was suspected Lactation was suppressed by hormone treatment

During the following three days the patient s condition deteriorated to generalized total paralysis She also had pains in all her extremities and in the muscles of her back Her neurological status remained largely unchanged for the next three weeks apart from a subjective impairment of hearing which lasted a few days

On 10th September the patient began to experience paraesthesiae in her hands and a few days later she was able to move her head slightly The paraesthesiae then regressed very slowly and breathing exercises could be started It was not until after 61 days (20th October) that respirator treatment could be stopped

During this period the patient was treated with various antibiotics owing to infection in the tracheostoma and also pneumonia She was given intensive physiotherapy

On 20th August CSF protein was 900 mg/l and on 27th August it was 4070 mg/l (CSF electrophoresis showed massive barrier damage with a serum like pattern) Virus cultures and titrations were negative

The patient was treated for a further four months at the Rehabilitation Department and was then able to leave hospital with only slight weakness of her extremities and vestigeal bilateral facial paresis Both babies were completely healthy when they left hospital

DISCUSSION

Only 28 cases of the Landry–Guillain–Barre syndrome during pregnancy have been reported and the diagnosis is uncertain in some of these (2 3 6–9 12 14 16 18–21 24–29) Several authors have claimed that the syndrome is very rare during pregnancy and it has been suggested that pregnancy per se protects the woman from LGBS (1 2 17 30) Ravn (26) after reviewing a large number of cases concluded however that the syndrome was not exceptionally uncommon in pregnant compared to non pregnant women Thus pregnancy does not seem to prevent the syndrome but nor does it influence the severity of the disease (19)

Osler & Sidell (20) suggested in1960 a number of diagnostic criteria for LGBS The case described here fulfils most of these criteria and the LGBS diagnosis may therefore be considered certain Similar symptoms with polyneuropathy or muscle weakness may occur during pregnancy due to nutritional deficiencies particularly vitamin B deficiency associated with hyperemesis gravidarum (17) In LGBS the facial nerve is the most affected cranial nerve and facial paresis during may be the only finding in very mild form of L (4)

In large series of patients with LGBS the mor ity has been between 10 and 20% increasing age The prognosis is considerably poorer w bulbar symptoms and respiratory depression present It has been possible however to red this high mortality to about half (13 26) by introduction of respirator treatment and impro antibiotic therapy

Of the 28 pregnant women with LGBS reporte the literature three died (11%) all post These three women were given respirator treatm at partus and two died later from infections and from haemorrhage from a tracheoarterial fistula 20 27)

The onset of LGBS in the previously descri pregnant women was not correlated to any part lar point of time during the pregnancy (29) course has been more serious when the onset curred during the latter part of pregnancy and r piratory failure has occurred in many of th cases In our patient the onset occurred in the 3 week of pregnancy without being preceded by m ifest infection The clinical course was unusu prolonged and severe Muscle weakness in the tremities and face was still evident six months a the onset In an unselected series of patients r sidual symptoms occurred in 5–10% (23) Mu function may however continue to improve fo to three years (22) According to the literature cranial nerves may be engaged except the olfa and vestibulocochlear nerves (26) Our pat complained of impairment of hearing but au metry could not be carried out and it was th fore not possible to verify objectively that the c lear nerve was involved The concentration of tein in the CSF was high (4070 mg/l) but th thought not to be correlated to the severity of disease (14 26)

Early spontaneous abortion occurred in on the 28 women suggesting that the frequency abortion does not increase in connection LGBS In cases in which onset of the disease curred during the first or second trimester the p nancy proceeded without complications in c cases and partus was normal When the onset curs during the third trimester however there increased risk of premature labour

It is well known that serious neurological

ases do not generally depress the uterine contractions and LGBS does not seem to be an exception to this The twin delivery took an obstetrically normal course in this case but suction had to be used during the expulsion phase Assisted extraction has been necessary in most cases in which paresis of abdominal muscles has been present Cesarean section has been used in three cases and two mothers both of whom were treated in a respirator died post partum whereas the third woman who had a mild form of LGBS at the time of partus survived

Since only a few cases of LGBS during the early part of pregnancy have been described in the literature it is not possible to draw certain conclusions as to whether or not the neurological disease is teratogenic No case of congenital malformations has been reported however

Of the 79 pregnancies (involving 30 foetuses/babies) complicated by LGBS that have been reported so far information is lacking for three infants Spontaneous abortion occurred in one case and one therapeutic abortion was performed in the ...enth week Twenty two babies survived and ... of these were premature Three babies died all shortly after partus from complications not definitely related to LGBS (7 19 28) The infant survival was thus at least 88 %

The mothers of the five surviving premature babies all fell ill during the final trimester The clinical course was severe and necessitated respirator treatment in all cases and two of these women died post partum None of the surviving infants has had symptoms of neurological disease and LGBS has thus not been transmitted from mother to offspring

In view of the good prognosis for the baby most authors consider that therapeutic abortion is not indicated Our twin birth supports this view

TREATMENT

Treatment of patients with acute polyradiculitis is symptomatic and in severe cases is aimed above all at maintaining adequate ventilation and preventing infection. The prognosis in patients with respiratory failure has also improved greatly since respirator treatment came into general use (26) Six out of 29 (21%) pregnant women with LGBS have required respirator treatment Whether the need for respirator treatment is greater in pregnant than in non-pregnant women is difficult to say Most published series of patients with LGBS are selected with a high proportion of severe cases

Steroid therapy was previously considered beneficial in certain cases (1 12 14) and Notter (19) used large doses of steroids without negative effects of the foetus More recent experience has not confirmed the effect of corticosteriods in LGBS however irrespective of whether the patient is pregnant or not (10 13 26) It is important that physiotherapy is given throughout the period of illness (5)

CONCLUSIONS

Only a few cases of LGBS in connection with pregnancy have been reported up to now In mild cases pregnancy does not seem to exacerbate the disease and the pregnancy often takes a completaly normal course The risk of malformations spontaneous abortion or foetal death seems not to increase In severe cases with complicating respiratory failure and onset during the last trimester however the risk to the mother and incidence of premature birth seems to increase greatly Most authors are agreed that abortion is not indicated either from the mother s or the baby s point of view Nor is there a stronger indication for cesarean section when the mother has LGBS Treatment is symptomatic only and there is no evidence that specific therapy such as corticosteriods is beneficial

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Submitted for publication May 19 1977

Greger Ahlberg
Department of Medicine
Falu Hospital
Falun Sweden

Acta Obstet Gynecol Scand 57 381–383 1978

RECURRENT HYDATIDIFORM MOLE

Report of a Case with Five Recurrences

Eva Patek and Per Johnson

From the Department of Obstetrics and Gynaecology Huddinge sjukhus Huddinge Sweden

bstract A report on a patient having five consecutive lar pregnancies is presented None of the pregnancies as associated with a fetus and all five hydatidiform moles ere histologically benign The treatment of recurrent les is discussed and the literature concerning this problem is reviewed

he occurrence of a hydatidiform mole is rare in dustrialized countries where it is reported to develop in the proportion of 1/2 500 pregnancies (5 7)

degenerations of pregnancy are more frequent in South East Asia and Latin America probably due to protein deficiency where its incidence is calculated to be 1/82 (8 9 11 12)

Recurrative hydatidiform mole is an extremely unusual condition with a reported incidence in the range of 1 in 75 molar pregnancies (13) The recurrent mole appears in two main patterns i e interspersion with normal pregnancies and the successive repetition of molar gestations (14)

The purpose of this paper is to present a case report of a patient with five hydatidiform moles to discuss the treatment and to review the literature concerning this subject

CASE REPORT

M. S aged 33 gravida 5 para 0 was first seen at Huddinge University Hospital in October 1976

1st pregnancy

Her first pregnancy occurred at the age of 24 She was treated for threatening abortion in the first trimester of pregnancy The patient started to bleed again in the 15th week and subsequently the uterus failed to grow In the 23rd week it reached the umbilicus and after slight bleeding the patient passed a bunch of grape like vesicles Evacuation was performed the same day and histological examination showed a benign mole HCG was within normal limits during the pregnancy and repeatedly negative after Arteriography of the pelvis was normal

2nd pregnancy

The patient was advised against pregnancy until a year had passed Her second pregnancy was uneventful except for intermittent vaginal haemorrhage The uterus was developing normally for the time of gestation and HCG was also normal During the last 6 weeks before admission however the uterus failed to enlarge fetal movements were never felt and at the 30th week of gestation the uterus reached the umbilicus X ray examination of the pelvis revealed no fetus and on the same day the patient spontaneously passed a hydatidiform mole which was histologically benign Arteriography 7 weeks later was normal and HCG negative

3rd pregnancy

The third pregnancy occurred ? years later The uterus failed to enlarge after the 15th week the patient had vaginal bleeding and suff red from hyperemesis However HCG values were within normal limits After the administration of ethinyl estradiol in the 30th week a hydatidiform mole was delivered and evacuation was performed The mole was histologically benign an arteriography was negative as were several HCG tests

4th pregnancy

The fourth pregnancy took place 1½ years later and was uneventful until the 18th week of gestation when the growth of the uterus ceased although HCG was normal Ultrasound in the 23rd week diagnosed a hydatidiform mole as did X ray of the pelvis After the administration of ethinyl estradiol and an intravenous oxytocin infusion a mole was passed and the uterus was evacuated The mole proved to be benign histologically and HCG was repeatedly negative A chromosomal analysis of the patient was now considered after the 4th consecutive mole but unfortunately not undertaken An X ray of the chest was negative

5th pregnancy

In her fifth pregnancy the patient had her last menstrual period on 1/7 1976 She was complaining of headache and hyperemesis and was suffering from slight intermittent vaginal bleeding Repeated vaginal examination disclosed that the uterus normally enlarged for the time of gestation until it reached the umbilicus when growth ceased The

uterus subsequently rather decreased in size. HCG was 185 000 IU/litre in the 14th week and 238 000 IU/litre in the 16th week. FHS were never heard and the patient had never felt any movements. In the 23rd week an ultrasound examination disclosed a picture typical of a hydatidiform mole. Labour was induced with oxytocin intravenous infusion and the uterine cavity was explored and evacuated by vacuum aspiration of typical grape-like moles. Histological examination of the specimen displayed a benign mole.

The family history of the patient showed that her sister had two children but had also had a hydatidiform mole. The patient and her husband have now decided against further pregnancies and in the belief of an increasing risk of development into a choriocarcinoma after each successive mole, sterilization will be performed as an elective hysterectomy. The family has applied for an adoptive child.

DISCUSSION

The repeat hydatidiform mole has always been considered to be an extreme rarity. Most such moles reported in the literature have only recurred twice (barely 60 cases reported with two recurrences), although as many as 18 repetitions in one and the same patient were reported by Essen-Moller in 1912 (5).

So far, only 43 cases, including that of our own, of a hydatidiform mole recurring 3 or more times have been reported (10, 12). However, many of the cases remain doubtful, as some instances of moles recurring more than six times were based only on the history offered by the patient and were not confirmed by any histological evidence. Moreover, some investigations were probably dealing with the growth of a persisting mole, rather than with a new pregnancy. In the present study, with 5 recurrent hydatidiform moles in the span of 9 years, there is evidence of the absence of molar tissue between each pregnancy.

The reported incidence of recurrent hydatidiform mole varies between 1 in 75 molar pregnancies (1.3%, Europe) (13) and 1/23 or 4.37% in another series (Mexico) (12). Incidences of 1/50 have been recorded by two independent groups, corresponding to a frequency of 2% (1, 11). This low incidence is partially explained by the fact that many patients are still treated with hysterectomy without previous curettage, as proposed by Acosta-Sison (1), and partly because a molar pregnancy is most common in the 5th decade, when a woman's fertility is low. Thus, it is not surprising that recurrent hydatidiform mole is uncommon, since less than half of the patients with molar degeneration bec[ame] pregnant again (4, 7).

Close observation of repeated molar pregnan[cies] for possible malignancy has been advocated [by] most authors (1, 4, 6–9). There is a suggestion [in] the literature that the trophoblastic malignancy [rate] might be higher in recurrent than in isolated mo[les] (1, 7–9). The incidence of choriocarcinoma [has] been calculated to be 7.9% after each mole [...]. The same author has calculated an incidence [of] choriocarcinoma/patient of 23% in repeat occur[rences]. This high incidence prompted several [in]vestigators to use cytotoxic agents as a prophyla[xis] against malignant trophoblastic disease in case [of] recurrent benign moles (8, 9). However, there [are] indications that these figures might be too h[igh]. The calculations were based on selected cases [and] some with a favourable outcome were lost [to] follow-up and thus omitted.

Brandes & Peretz (2) have suggested that [the] term 'habitual mole' should be used after 3 m[oles] as 'habitual abortion' is used after 3 abortio[ns]. They postulated that this might be an entirely [dif]ferent entity, as no chorionic malignancy [has] hitherto been reported in patients where hydatidiform mole has recurred more than tw[ice]. They suggested that the rate of chorionic [ma]lignancy might decrease even to extinction [in] cases of recurrence on 3 or more occasions. [It is] also striking that in these cases with 'habi[tual] mole' a normal pregnancy interspersed in the [series] of moles is very rare.

A series of 43 known cases of 'habitual mol[e]', some of them even doubtful, is too small to d[raw] any conclusions as to their possible malignant [out]come. It is therefore advisable to treat each in[di]vidual case on its own merits. Close surveillanc[e is] necessary in all cases, but hysterectomy can[not be] recommended after a certain arbitrary number [of] moles, unless other criteria warrant it.

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Submitted for publication Feb 21 1977

Eva Patek
Huddinge Hospital
S-141 86 Huddinge
Sweden

Acta Obstet Gynecol Scand 57 385–387 1978

GRANULAR CELL MYOBLASTOMA OF THE VULVA
REPORT OF 4 CASES

Ram Dgani Bernard Czernobilsky Richard Borenstein and Moshe Lancet

the Department of Obstetrics and Gynecology and the Department of Pathology Kaplan Hospital Rehovot Israel Affiliated to the Medical School of the Hebrew University and Hadassah Jerusalem Israel

Granular cell myoblastoma is a rare tumor for which the vulvar area is one site of predilection It occurs at any age as a firm rounded nodule usually not exceeding 3 cm in diameter (10) The current view is that this tumor may be derived from Schwann cells (4 8) Only 49 cases of granular cell myoblastoma of the vulva have so far been reported (3 6)

CASE REPORTS

Case 1 The patient a 6? year-old Jewish female gravida para 3 aborta 1 was seen on November 3 1975 in the gynecologic clinic because of a lump on the genitalia noted for approximately 6 months The lump had caused no pain but it was itching A firm nontender 3 mm tumor was noted on the middle portion of the right labium majus The tumor was freely movable

The preoperative impression was that of a sebaceous cyst The tumor was excised with a border of normal tissue Upon section it was seen to be firm pale yellow homogenous and apparently not encapsulated This was consistent with the description of granular cell myoblastoma in the literature The patient has been followed for 18 months without local recurrence or appearance of a similar tumor elsewhere

Case 2 This 56-year-old Jewish female gravida 4 para 3 aborta 1 was seen in December 1976 with the complaint of a slowly growing lump on the genitalia noted for approximately 1 year The tumor measuring 2 cm in diameter was located on the anterior portion of the left labium majus was hard and not tender The impression was that it was a lipoma

The lesion was excised with a 1 cm border of normal tissue The tumor presented the same gross features of a typical granular cell myoblastoma

No recurrence has been noted in a 6-months follow up

Case 3 This 17 year-old single Jewish female presented herself in May 1976 for treatment of a recently noticed lump on the genitalia. Physical examination revealed a firm nodule ? cm in diameter involving the right labium majus Under local anesthesia wide excision of the nodule was performed The tumor showed the macroscopic details of a granular cell myoblastoma During the year since her operation no recurrence has been noted

Case 4 A 35 year-old Jewish female gravida 4 para 4 was seen in August 1971 because of vulvar lump that appeared one year before and has increased in size recently A firm 1 cm × cm nodule was noted on the left labium majus

The tumor was excised with a border of normal tissue The cut surface was grossly similar to those described above but it was whitish There has been no evidence for recurrence during the ensuing 5 years

Histologic examination of the 4 tumors revealed a similar picture in all of them It consisted of large cells with a finely periodic acid S hiff positive granular cytoplasm and small round centrally placed regular nuclei The cells had poorly defined cytoplasmic borders The lesions were present within the dermis and subcutaneous tissue and lacked encapsulation The overlying squamous epithelium demonstrated some areas of irregular proliferation in cases 2 and 4 The tumors were all completely excised (Figs 1–?)

COMMENT

Only about 7% of the granular cell myoblastoma have been located in the vulva About 35% of these tumors have involved the tongue and the rest have been found in the skin and various other sites Age incidence has varied from 6–70 years (2 3)

On clinical examination a granular cell myoblastoma presents generally as a small solitary painless mass and may be similar to lipoma fibroma hidradenoma papilloma sebaceous cyst and Bartholin gland tumor (2) If ulceration of the overlying skin occurs it may simulate carcinoma or venereal disease (3) Multiple tumors are reported in 3–16% of cases This tumor may recur locally and



Fig 1 Vulvar tissue showing some irregular proliferation of the overlying squamous epithelium and diffuse infiltration of dermis and subcutaneous tissue by ill-defined cells with small round nuclei Hematoxylin Eosin ×100

rarely may be malignant (6 9) In such cases metastatic spread occurs in general by lymphatic channels and causes death regardless of therapy (5 6)

Recent evidence has suggested that this tumor is of neural origin Electron microscopy and histochemical studies of the tumor revealed similarity t Schwann cells and it was felt that granular ce myoblastoma is a misnomer and the tumo appropriate name should rather be granular ce Schwannoma (4 8) Previous reports of granula cell myoblastomas which were found within th

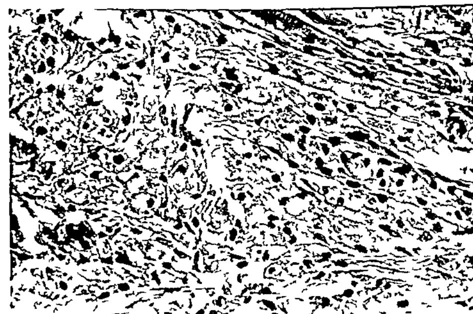


Fig 2 High magnification of granular cell myoblastoma showing typical granular cytoplasm and centrally placed nuclei of cells Hematoxylin Eosin ×250

sheath of peripheral nerve (1) and within the hypophyseal stalk (7) have supported a neural histogenesis The accompanying hyperplastic response of the overlying squamous epithelium may occasionally simulate a squamous cell carcinoma (6 10)

The tumors are radio resistant usually not encapsulated and may recur locally Therefore wide local excision was recommended as the treatment of choice (3) If a malignant granular cell myoblastoma is found radical vulvectomy with regional node dissection should be considered Radiation therapy or chemotherapy has little or no value (6)

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Submitted for publication August 8 1977

Moshe Lancet
Department of Obstetrics and Gynecology
Kaplan Hospital
Rehovot
Israel

ANNOUNCEMENTS

IUD and Biodegradable Delivery Systems (International Symposium Amsterdam Holland June 28–30 1979)

Thirty leading andrologists gynecologists and reproductive biologists have been invited to discuss

I Kinetics & Application of IUD Copper IUD Steroid delivery systems for contraception Failure rate of IUD IUD and pregnancy IUD expulsion and related phenomena Post placental IUD insertion IUD and family planning IUD and inflammatory diseases Future development of IUD and Management of intraperitoneal IUD

2 Physiology and Biochemistry Geometry of IUD and uterine lumen Physiology of uterine blood loss Physiological mechanisms of endometrial bleeding in the IUD s Pathology of endometrial bleeding by IUD Factors affecting uterine blood loss Fibrinolytic agents Immobilization of spermatozoa Agglutination of spermatozoa

3 Biodegradable Delivery Systems Biodegradable polymers polyactides and polyglycolides Kinetics of release diffusion and erosion Biodegradable microcapsules and microspheres Use of bioenerts bioactive and biodegradables Toxicology and teratology of local delivery systems Homo and copolymers as biodegradable delivery systems Device design and system application Antifibrinolytic agent release from IUD Multidimensional models for estimating & predicting IUD-related menstrual blood loss Decision system for selecting best IUD for individual acceptors Biodegradable polymers to improve postpartum IUD retention

This is a satellite symposium of PANCA to be held March in Caracas Venezuela Program Directors J van Os Haarlem Holland & E S E Hafez Detroit US Symposium Office Miss K Spanjaard P O Box 70 53 Oss Holland telex 50959

Xth World Congress of Fertility and Sterility

The International Federation of Fertility Societies will sponsor the Xth World Congress to be hosted by the Spanish Fertility Society at the National Palace of Expositions and Congresses in Madrid Spain September 20–26 1980 There will be sessions on Contributions to the Themes New Methods Workshops Luncheon Conferences Informal Sessions of Questions and Answers by expertees Scientific Exhibits Motion Pictures etc There will be two days for Pre Congress Symposia and Post Graduate Courses followed by a program on the following themes

I Spermatogenesis (Induction and inhibition clinical and physiological aspects)

II Ovulation (Induction and inhibition clinical and physiological aspects)

III Psychosexual and social aspects of fertility (Psychosexual social)

IV Problems of gametes transportation (Female male)

V Immunology in reproduction (Female male)

VI Control of fertility (Female male)

VII Neuro-endocrinology of reproduction (Female male)

VIII Fertilization and implantation (Fertilization implantation)

IX Environmental and iatrogenic aspects of reproduction (Environmental factors iatrogenic factors)

X Genetics in reproduction

Send inquiries to

Scientific Program Chairman Prof A Campos da P[illegible] M D Av N S de Copacabana 664/607 Rio de Janeiro 20000-Brazil

President of the Congress Dr J Cortes Prieto M D Pto Bermeo 11 (Mirasierra) Madrid 34 Spain

President of IFFS Dr P C Steptoe M D 61 [illegible] Street West Oldham Lancs England

Acta Obstet Gynecol Scand 57 389–392 1978

EFFECT OF CHLORTHIAZIDE TREATMENT ON RENIN–ALDOSTERONE SYSTEM DURING PREGNANCY

Risto Lammintausta Risto Erkkola and Matias Eronen

From the Institute of Biomedicine Department of Pharmacology University of Turku and the Department of Obstetrics and Gynecology Turku University Central Hospital Turku Finland

Abstract Plasma renin activity and urinary excretions of aldosterone sodium and potassium were studied before and during one weeks s chlorthiazide treatment in eight women with a slight peripheral oedema in the 31st week of pregnancy Plasma renin activity and excretion of aldosterone increased clearly on the first day of treatment but on the 7th day it was more than doubled in comparison with the level before the treatment Diuresis and excretion of sodium increased promptly on the 1st day but did not differ from the level found before the treatment on the 7th day The high reserves of renin and aldosterone secretion found in this study may be regarded important in ensuring blood pressure plasma volume and placental flow during pregnancy

In the obstetrical literature contradictory statements exist on the usefulness of diuretic treatment during pregnancy In some studies the prophylactic use of diuretics has been shown to decrease the incidence or severity of toxemia and also the perinatal mortality (8 13) whereas other investigators have found diuretics of no value or even harmful (3 4) Diuretics are however in common use and there are areas in which more than half of the mothers receive this kind of therapy during their pregnancy (9)

The thiazide diuretics are known to activate the renin-aldosterone system (6 16) In one of our earlier studies (1?) we demonstrated how the pregnancy also activates this system In the 30th week of pregnancy the plasma renin activity (PRA) was increased approximately seven fold and aldosterone excretion in urine approximately 13 fold compared to non pregnant excretion

This in mind we planned and carried out our study firstly to observe the effect of diuretics on the renin-aldosterone system during pregnancy and secondly to detect whether the raised values of pregnancy could be increased any further

SUBJECTS AND METHODS

Eight women with slightly oedematous ankles volunteered to take part in this study The mean age weight blood pressure taken when the subject sat up as well as the length of pregnancy are recorded in Table I Four of the mothers had delivered one child and four were nulliparae None of the mothers suffered from any disease The course of the pregnancy was uneventful and apart from iron tablets none of them received any treatment Each mother carried out her ordinary daily routine during the study period

On the first day of the study the women collected a 24 hour urine specimen starting at 7 a m At 1 p m a venous blood sample was withdrawn The following morning when the women brought their first urine samples at 7 a m each was given a 500 mg tablet of chlorthiazide (Salutrid® Leiras Finland) after which they started the new 24 hour urine collection At 1 p m they came for blood sampling they also received six more chlorthiazide tablets and were told to take one tablet each subsequent morning On the 7th day they took the last tablet at 7 a m and began to collect the last 24-hour urine sample At 1 p m they had their last blood sample taken A special diet was not given but the women were instructed not to alter their dietary habits during the study The women fasted for two hours before blood sampling

The 5 ml blood sample for PRA was always withdrawn into an EDTA tube chilled in ice water Plasma was separated at 10 min by refrigerated centrifuge at +4 C and stored at −20°C until analysis For the PRA the angiotensin I generated by plasma renin in one hour at 37°C at pH 6 0 (maleate buffered) was determined by radioimmunoassay (12) and expressed as ng angiotensin I/ml/hour

The volume of the 24-hour urine samples were measured and the daily excretions of aldosterone sodium and potassium were determined Free and acid labile glucuronized aldosterone in the urine were determined by radioimmunoassay by using first the method of Bayard et al (1) for hydrolysis and extraction and then the method of Ekins et al (5) for chromatographic purification Urinary sodium and potassium were determined using an atomic absorption spectrophotometer (Varian Tectron Model 1100) The intra assay p ion (SD) of 10 samples

Table I The subjects participating in the study (n=8)

	Mean	S E M	Range
Age (years)	25 3	1 6	20– 31
Weight (kg)	77 4	4 0	69– 90
Duration of pregnancy (weeks)	31 3	0 7	29– 35
Systolic blood pressure (mmHg)	127	3	120–130
Diastolic blood pressure (mmHg)	77	3	70– 90

in the same series was 0 38 for PRA at the level of 4 5 ng/ml/h and 5 5 for aldosterone at the level of 65 7 μg/day The inter assay precision (SD) for the PRA in 17 different series was 0 15 at the level of 1 14 ng/ml/h

RESULTS

The PRA (Fig 1) on the day before treatment was 15 2±1 2 (S E M) ng/ml/h The level reached 6 hours after the first tablet was already significantly increased ($p<0\ 05$) On the last day of the study the level was 31 3±4 8 ng/ml/h The difference compared to the pre treatment value is significant ($p<0\ 01$)

The urinary excretion of aldosterone (Fig 1) before treatment was 55 9±10 4 μg/24 hours In the 24 hours after the first chlorthiazide tablet the excretion was higher ($p<0\ 05$) and on the 7th day it was 117 0±9 8 μg/24 hours significantly higher than pre treatment excretion ($p<0\ 001$) The increase in aldosterone excretion during the first day correlated positively with the corresponding PRA increase (Table II)

The urinary excretion of sodium (Fig 2) increased from 102±19 mmol/24 hours to 131±21 mmol in the 24 hours after the first tablet ($p<0\ 05$) but the excretion of sodium in the 7th day had decreased to 115±11 mmol/24 hours and thus no longer differed from the pre treatment excretion The higher the pre treatment excretion of sodium the less the excretion increased on the first and the 7th day (Table II) The increase in PRA from the pre treatment to the 7th day was in positive correlation with the corresponding increase of sodium excretion (Table II)

The urinary excretion of potassium did not change significantly during the treatment but a slight tendency to rise is evident (Fig 2) The increase of potassium excretion before treatment to the first day showed a positive correlation with the

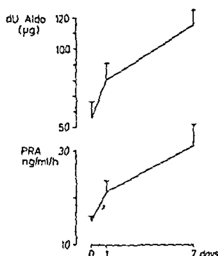


Fig 1 Mean levels (± S E M) of plasma renin activity (PRA) and daily urinary excretion of aldosterone (dU Aldo) before and in the first and seventh day of chlorthiazide treatment during pregnancy * =<0 05 **=p<0 01 *** =p<0 001

increase of aldosterone excretion (Table II) The ratio of excretions of sodium and potassium increased from 2 2±0 2 to 2 8±0 3 in the first day ($p<0\ 01$) but decreased to the level of the pre treatment day in the 7th day

The volume of the 24 hour urine was significantly greater in the 24 hours after the first tablet of chlorthiazide ($p<0\ 01$) On the 7th day however the urine excretion was lower ($p<0\ 05$) than on the first day of the treatment and did not differ any longer from the pre treatment day excretion (Fig 2)

DISCUSSION

In our earlier study we found a non pregnant PRA level of 2 2±0 3 ng/ml/h (n=27) (17) In the 30th week of pregnancy we found the level of 15 ±2 ng/ml/h (n=10) which is the same level as we found in this study on the pre treatment day During the chlorthiazide treatment the PRA level doubled within one week In non pregnant subjects a similar increase was noticed during the first week of diuretic treatment (16) but the initial levels were considerably lower In these cases the renin is of renal origin In pregnancy the PRA level is much higher It seems unlikely that all the renin is released from the kidneys and production in the placenta and membranes has been suggested (10 11)

The increased excretion of sodium and cor

Table II *Coefficients of linear correlation (r) between the diuretic induced changes of PRA dU–Aldo dU–Na and dU–K*

Abbreviations as in Figures

	dU–Aldo	dU–Na	dU–K
PRA	0 693 (0–1 day)	0 823 (0–7 days)	
dU Al o		0 595 (0–1 day)	0 8 6 + (0–1 day)
dU Na		0 870 (/0–1 day)	0 923 + (0–7 days)
dU Na		0 876 (/0–7 days)	

...ificant decrease in the body exchangeable sodium which leads to a decrease of plasma volume during diuretic treatment might be one possible explanation for the increase of PRA (15) It is likely that this decrease in plasma volume leads to a decrease in placental perfusion and—as a reaction—renin may be liberated from the fetoplacental unit. This renin release could be significant in the maintenance of maternal blood pressure and consequently in the maintenance of the placental perfusion (7)

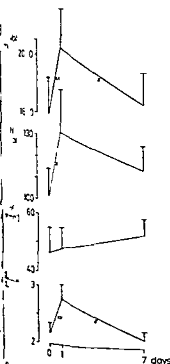


Fig 2 Mean levels (± S E M) of daily urinary excretion (dU–Vol) excretion of sodium (dU–Na) and potassium (dU–K) and sodium–potassium ratio before and in the first and seventh day of chlorthiazide treatment during pregnancy

According to the earlier findings presented in one of our studies (12) the aldosterone excretion of non pregnant women as 3 7±0 3 μg/24 hours ($n=27$) and in the 30th week of pregnancy 47 9±13 0 ($n=10$) In this study the aldosterone excretion in the 31st week was 55 9±10 4 on the pre treatment day but it was also more than double on the 7th day of the chlorthiazide treatment It is likely that the increase of progesterone level during pregnancy is the stimulator of aldosterone secretion (14) Without high levels of aldosterone the pregnant woman would lose—due to her progesterone alone—all her exchangeable sodium into the urine within about four hours (2)

In this study the addition of exogenic diuretic effect to the progestational effect in the kidneys required a doubled aldosterone secretion an equally high level is found only in Conn s syndrome Urine output increased rapidly at the onset of diuretic treatment and then gradually decreased This has also been observed in non pregnant subjects (16) The increase in aldosterone secretion could be the results of the increased sodium excretion and mediated by the rise in renin secretion During pregnancy the hypokalemic effect of saluretics is well established and this can be assumed to be due largely to the increased aldosterone secretion In this study no significant rise of potassium excretion was detected but the correlation between the increases of aldosterone and potassium excretions was positive

Clinically it is concluded that after a week s treatment with chlorthiazide the urine output is at the same level as before the treatment If further increase is needed it probably can be brought about by using aldosterone antagonists With diuretic treatment the plasma volume decreases at least temporarily while as a reaction PRA rises this may minimize a possible decrease in the placental blood flow

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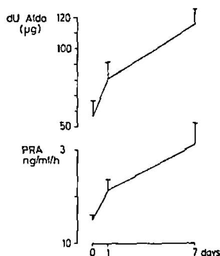


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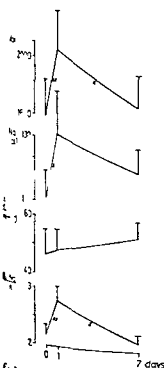


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Table I *The modified Bishop score used in the present investigation*

	Score rating		
	0	1	2
Cervical dilatation	<0 5	0 5–1 5 cm	>1 5 cm
Cervical effacement	None	<50%	>50%
Station of fetal head	Above or in pelvic inlet	Above spines	At or below spines
Cervical consistency	Firm	Medium	Soft
Cervical position	Posterior	Medium	Anterior

gestational age (Table III) None of the patients had suspected cephalopelvic disproportion or breech presentation All had intact membranes

Preparation of PGE₂-gel

A solution of PGE_2 was prepared by mixing PGE_2 powder (Upjohn) in ethanol The solution was sterile filtered and kept at −20 C The viscous medium was prepared by mixing 3 0 g hydroxypropylmethyl cellulose with 100 ml hot water The mixture was autoclaved at 120 C for 20 minutes After cooling and shaking the viscous medium was divided into 5 ml portions and stored in small glass containers The clinically used PGE_2 gel was prepared immediately before use by mixing 0 2 ml PGE_2 solution (1 0 mg) with 4 ml of the viscous medium

Experimental procedure

All patients had ultrasound scanning of the uterus performed before the investigation was started By this procedure the localization of the placenta the configuration of the uterus and the size and position of the fetus were determined Patients with low implanted placentas were excluded from the study On the morning the day before planned induction the cervical state was determined always by the same investigator according to a modified Bishop score (Table I) With the patient in the lithotomy position the PGE_2 gel was administered intracervically via a 12 cm long catheter with an outer diameter of 3 3 mm The gel was placed as far as possible into the cervical canal—as a rule close to the internal os After application of the gel the catheter was withdrawn and the patient was requested to stay in bed for 2 hours

All patients remained under supervision in the antenatal ward Pulse and blood pressure were recorded intermittently The patients were asked to comment on the eff of the treatment including possible side effects In m patients uterine contractions were monitored by ext tocometry (Hewlett Packard or Roche) If the treatm induced regular myometrial contractions affecting t cervical state the patients were moved to the delive ward and supervised using routine techniques such external or internal cardio-tocography and repeated p measurements from the fetal scalp In the patients whom labour was not induced or if the contracti waned the cervical state was reassessed the follow morning before the induction of labour with intraveno oxytocin

Table II *Results of intracervical instillation of 1 mg PGE_2 in the patients of Group A*

	Delivered after primary induction (n=23)	Undelivered after primary induction (n=18)
Nulliparae	10	10
Multiparae	13	8
Bishop score before instillation	3 3 (1–5)	2 5 (0–4)
Bishop score after instillation	–	6 1 (4–8)

RESULTS

Group A

All 41 patients experienced uterine contractio within half an hour after PGE gel administratio Twenty three (56%) progressed without furth stimulation into established labour within 6 hour In the mean delivery occurred after 10 hours (ran 4 to 15 hours)

Table II gives the effect on the cervical state the 18 patients of group A in whom uterine contra tions did not progress into established labour Th Bishop score changed during 24 hours from 2

Table III *Clinical data of the patients in Group and results of the double blind study*

	Gel with placebo (n=10)	Gel with PGE_2 (n=10)
Nulliparae	10	10
Mean age	25 (18–33)	4 (18–35)
Mean gestational age (weeks)	41 (39–43)	40 (38–4)
Mean Bishop score before instillation	3 6 (2–5)	3 5 (5)
Mean Bishop score 24 hours after instillation	4 0 (–6)	6 and 7 (2 patients) o
Delivered after primary induction	0	8

[illegible] 0 to 4) to 6 1 (range 4 to 8) Fourteen of the 18 women had labour induced successfully with an intravenous oxytocin infusion the day after PGE_2 administration The time to delivery was 8 hours (4 to 17 hours) Concerning the other 4 patients 1 was delivered after a second infusion with intravenous oxytocin and 1 went into spontaneous labour 2 days after the first trial In 2 patients the membranes ruptured spontaneously 2 days after the first induction they were successfully stimulated with intravenous oxytocin and delivered uneventfully

Group B

All patients who were given active gel (the gel containing 1 0 mg PGE) experienced uterine contractions within half an hour In 8 patients the contractions progressed to established labour and they were delivered without further stimulation within 10 hours (range 5 to 13 hours) after the application of the gel In 2 patients contractions waned after about 3 to 4 hours

The cervical state changed from a Bishop score of [illegible] to 6 and 7 respectively during 24 hours In these two patients labour was induced the morning after PGE_2 administration by means of oxytocin infusion and delivery occurred successfully after 8 and 10 hours

In the 10 patients receiving placebo gel (gel without PGE_2) only 2 experienced uterine contractions within half an hour The contractions disappeared completely after about 2 hours At examination the next morning before induction the mean Bishop score was 4 0 compared with 3 6 before the application of the gel In the remaining 8 patients no [illegible]ne contractions or consistent change in Bishop score were noticed during 24 hours (Table III)

Three patients receiving placebo gel were induced successfully with intravenous oxytocin the [illegible] after the gel administration The time to delivery was 10 13 and 17 hours In the remaining 7 patients the first oxytocin induction failed However all were successfully induced and delivered within 1 week of the trial

In group A 5 patients (12 %) were delivered by vacuum extraction because of fetal distress in the second stage of labour Four of the children had 5 minute Apgar scores of 8 to 10 but the remaining child had an Apgar score of 3 There were no problems at the induction of this patient who went into established labour 3 hours after application of the gel She was supervised routinely in the delivery ward and labour was normal until late second stage Then a marked fetal bradycardia occurred and a vacuum extraction was performed At delivery the child had a severe bradycardia and was cyanotic and hypotonic The child died after 2 hours despite intubation and ventilation with oxygen The subsequent autopsy revealed intracranial hemorrhage

All patients receiving active PGE_2 gel in group B were delivered vaginally The children had 5 minute Apgar scores of 9 or 10 Four patients in group B receiving placebo gel had to be instrumentally delivered 3 by Caesarean section because of prolonged labour and 1 by vacuum extraction because of fetal distress in the second stage of labour The infants of the patients receiving placebo gel had 5 minute Apgar scores of 8 to 10

In all patients in whom uterine contractions progressed into established labour and in whom delivery occurred without further stimulation there was no need for analgesia No signs of uterine hypertonus or abnormal myometrial activity were observed There were no complaints of gastrointestinal discomfort and no marked changes in pulse rate or blood pressure were recorded In one patient there was a transient increase in temperature from 37 5 C to 38 2°C This patient also had a short period of shivering

DISCUSSION

Priming or ripening of the uterine cervix before induction of labour by means of PGE_2 in a viscous medium applied locally has recently been reported by several investigators e g Shepherd et al (1976) Calder et al (1977) Thiery et al (1977) and MacKenzie & Embrey (1977) The doses used when administering the prostaglandin extraamniotically have generally ranged between 250 and 500 μg Calder et al (1977) suggested that the optimum priming dose of PGE_2 is about 400 μg However because of failure of induction or unimproved cervical state they considered that a larger dose might have been more effective in some patients Twenty four of their 121 patients (20 %) were either delivered or established in labour on the morning after PGE_2 administration In the remaining 97 patients the cervical score had improved from a mean of 2 3 to 6 3

In the present investigation a dose of 1 mg was deposited intracervically This resulted in a higher frequency of successful inductions with PGE_2 than

in the study of Calder et al (1977) 31 of 51 patients (61 %) were delivered within 15 hours The cervical improvement in undelivered patients and the frequency of Caesarean section were similar It is probable that the difference in the incidence of successful induction is related to the difference in dose The frequency of fetal distress in the second stage of labour (5 in 51 patients) in the present study might also have some relation to the dose Even though no signs of uterine hypertonus occurred in our patients a smaller dose might have been sufficient Like Calder et al (1977) we feel that the dosage could be adjusted to the cervical score

Passing a catheter through the cervical canal to deposit viscous medium was demonstrated to have a negligible effect on the state of the cervix by Shepherd et al (1976) The present results fully confirmed this finding as the patients receiving gel without PGE_2 showed no consistent changes in their cervical state

The mode of action of the locally administered PGE_2 on cervical tissue is not known According to Danforth et al (1974) cervical dilatation during labour is an active process involving changes in cervical composition They found that in the cervix immediately after delivery there was a slight increase in water a marked decline in collagen and glycoprotein and a marked increase in glycosaminoglycans In addition a new component of unidentified nature was isolated Using an in vitro model Conrad & Ueland (1976) found that PGE_2 reduced the cervical connective tissue stiffness They investigated only the dense collagenous core of the cervix which excluded effects on the muscle layer Studies by Coutinho & Darzé (1976) on cervical mechanical activity in vivo suggest that PGE_2 has a direct relaxing effect of the smooth muscle of the non pregnant uterine cervix This agrees with in vitro studies by Najak et al (1970) which showed that spontaneous contractile activity of the cervical muscle layer was increased by PGF_2 and decreased by PGE_2

The present study confirms previous reports that local administration of PGE_2 in a viscous medium can induce ripening of the cervix and may sometimes induce labour in patients reaching term with an unfavourable cervical state

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Submitted for publication Oct 25 1977

Ulf Ulmsten
Dept of Obstetrics and Gynaecology
University Hospital
S 21401 Malmö Sweden

Acta Obstet Gynecol Scand 57 407–410 1978

INTRAUTERINE SUPRAVENTRICULAR TACHYCARDIA

N H Valenius and J Ramsøe Jacobsen

From the Department of Paediatrics TG Queen Louise s Hospital for Children and Department of Neonatology GN Rigshospitalet University of Copenhagen Denmark

[illegible] Four cases of intra uterine ectopic supraventricular tachycardia are described In three there were none or only minor symptoms immediately after delivery and subsequently The fourth baby having a congenital W P–W syndrome was born with severe hydrops fetalis and was asphyxiated From these cases and from data reported in the literature it is concluded that intrauterine heart failure is a significant risk when the fetal heart rate persistently exceeds 230 per minute It is suggested that digoxin administered to the mother may be beneficial to the fetus in cases of intra uterine ectopic tachycardia

Less than 50 cases of intrauterine supraventricular tachycardia (IT) have been reported In a review [illegible]kuff collected 17 cases and he concluded that IT was most often well tolerated by the fetus (18) However several recent reports have stressed that IT may result in severe intrauterine cardiac failure the babies being born with hydrops fetalis or developing severe cardio respiratory distress immediately after birth (11 22 27)

It is the purpose of the present communication to [illegible] s the identification of the cases of IT at risk of developing intrauterine complications from a review of the literature and from the observations in [illegible] new cases

CASE REPORTS

Case I A girl born 1966 Four weeks before term the fetal heart rate was found increased by auscultation One week before term a fetal ECG demonstrated a regular tachycardia of [illegible]00/min As the tachycardia persisted a caesarean section was performed 5 days later The baby was slightly depressed with an Apgar score of 5 at 1 min but 9 at 5 min Birth weight 3450 g An ECG confirmed the [illegible] of supraventricular tachycardia of 200/min (16) After digitalization the tachycardia became repetitive i e [illegible] alternating with short episodes of sinus rhythm The tachycardia continued until the age of 13 [illegible] and caused no symptoms This patient was previously reported elsewhere (16)

Case II A boy born 197? 3½ months prior to term a fetal tachycardia of 240/min was noted by the home physician During the remaining part of the pregnancy the fetal heart rate was consistently observed to alternate between ?40 and 140 per min The delivery was spontaneous and uncomplicated at term The baby was well with an Apgar score at 10 at 1 min Birth weight 3 100 g An ECG showed short sequences of sinus rhythm of 160/min alternating with paroxysms of supraventricular tachycardia of ?40/min lasting from 10 to 60 sec Due to mild tachypnea digoxin was administered from the second day of age followed by gradual disappearance of the tachycardia Digoxin was discontinued at 7 days of age but resumed as two isolated paroxysms were observed three days later No further tachycardia was noted not even after discontinuation of the treatment at the age of 6 months

Case III A boy born 1973 Two weeks prior to term the mother had a routine examination at hospital and nothing abnormal was disclosed During the following two days the mother noticed absence of fetal movements and contacted the hospital A fetal tachycardia of 248/min was observed It persisted for the following 4 hours and caesarean section was performed on the suspicion of fetal distress The delivery was difficult and the baby was severely asphyxiated with an Apgar score of 3 at 1 and 3 min and 7 at 15 min There was no tachycardia During vigorous resuscitation several episodes of bradycardia and asystole were observed until the heart rhythm settled at 140/min at 15 min of age Birth weight 3850 g There was extensive oedema including ascites hydrothorax and pulmonary rales The infant was treated in an incubator with oxygen digoxin and frusemide The blood sugar was found to be zero and was corrected with intravenous glucose The ECG (Fig 1) revealed sinus rhythm with Wolf Parkinson White syndrome (WPW) or pre-excitation type A an anomaly frequently associated with paroxysmal supraventricular tachycardia No blood group incompatibility was revealed At 8 hours the supraventricular tachycardia recurred at a rate of ?50/min Practolol 1 mg i v had no effect As the blood sugar was low again 0 7 mmol/l sampled prior to the administration of practolol glucose was given i v and during the injection the tachycardia reverted into sinus rhythm The infant lost 780 g during the first three days of life He presented no further cardiac problems but the course was complicated by fits and cerebral hemorrhage At the age of one year there were signs of spastic diplegia blindness and mental retardation The ECG demonstrated WPW syndrome un[illegible] age of 10 weeks and later only normal sinus rhy[illegible]

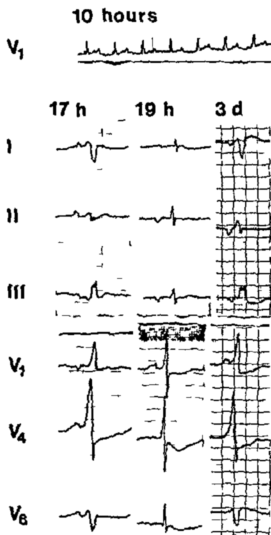


Fig 1 ECG in case III showing atrial tachycardia of 250 per min at 10 hours sinus rhythm with preexcitation at 17 hours ectopic (left) atrial rhythm with normal ventricular activation at 19 hours and preexcitation at 3 days of age

ever since the age of 6 months he has had recurrent paroxysmal supraventricular tachycardia despite treatment

Case IV A girl born 1975 The mother was admitted to hospital at term because of decreasing estriol excretion The fetal heart rate was 136/min On the following day the mother noticed absence of fetal movements and a fetal tachycardia of 260/min was revealed A few hours later fetal movements returned but the fetal heart rate was not recorded Two days later a caesarean section was performed because of a breech presentation and a maternal age of 40 The baby was well at birth but the heart rate was found to be 300/min An ECG confirmed the presence of supraventricular tachycardia Digitalization was instituted and sinus rhythm returned within the next 24 hours The ECG now demonstrated WPW syndrome The baby remained in excellent condition until the age of 7 weeks when she was admitted after a syncope Continuous ECG monitoring in hospital revealed intermittent arrhythmia and atrioventricular conduction d... suggesting digitalis toxicity Digoxin was withdrawn she had no further symptoms From the age of 3 m she has had normal sinus rhythm without WPW syndrome

DISCUSSION

The four cases demonstrate the variable outcome IT While cases I II and IV had none or very symptoms only immediately after birth case I presented with hydrops fetalis and seve asphyxia probably as the result of intrau failure This patient and patient IV also had W-P-W syndrome which has been reported on once previously in a case of IT (11) There are previous reports of IT associated with hydro fetalis (22 27) and in another three cases i hydrops (5 14 17) an ectopic tachycardia observed immediately after birth One patient wi hydrops fetalis from an unknown cause devel paroxysmal arterial tachycardia at 17 days of (6) and it was suggested that the hydrops had caused by IT IT should thus be listed among possible causes in cases of unexplained h fetalis

The development of heart failure in paroxys atrial tachycardia in infants is common and ered related to the extremely high heart rates ally encountered i e 250–300 per minute and the duration of the paroxysms The heart rates in I have most often been reported to be variable e due to an intermittent tachycardia or to a ... ventricular block typically seen in atrial flutter also in some cases of atrial tachycardia As ... termittently normal or even reduced heart rate ma lead to some recovery from heart failure the ... heart rates reported in 36 cases of IT (1–4 7 13 18–22 24–31) were analyzed for a possible relat to the immediate symptoms at birth All 6 patient with heart rates persistently above 230 per minut had severe symptoms at birth with an Apgar scor less than 7 at 1 min and presenting with ... hydrops (27) moderate edema and cyanosis (11) o severe respiratory distress (11 18 31) Of the re maining 30 patients 6 had severe symptoms on presenting with hydrops (22) and the remain with edema cyanosis and tachypnoea (11 13 19) In three of these (12 13 19) the lowest reporte heart rate was above 200 per minute

The duration of the tachycardia cannot be of ...

...gnostic importance as it will usually be unknown at the time of diagnosis. Thus the observed duration of IT in three patients presenting with hydrops ...ed between minutes (22) and 33 days (27) and was probably 2 days in our case III. Eight cases in addition to our case (no. II) had IT for more than 1 month (?, 8, 9, 17, 26–29) and only one of these babies (27) had symptoms at birth.

Before the introduction of electroconversion digitalis was the main treatment of paroxysmal tachycardia in infants, usually alleviating the concomitant heart failure and possibly promoting conversion to sinus rhythm. Digitalis is also commonly used for the prevention of recurrences. Digoxin readily crosses the placenta, the serum level in cord blood being identical to the maternal serum level when in maintenance treatment (23). Toxic serum levels are higher in infants than in adults. Thus it appears likely that digitalization of the mother aiming at the therapeutic serum level of 0.5–1.5 ng/ml will be of no harm and of possible benefit to the fetus having IT. No such therapeutic approach has been reported in the literature but it deserves consideration in those cases in which it is decided to continue the pregnancy.

From the four cases reported here, and from the data obtained from the literature, it can be concluded that IT is most often well tolerated. There is, however, a risk of intrauterine heart failure when the fetal heart rate persistently exceeds 200/min and the risk becomes high when the heart rate rises above 230/min. It does not seem warranted to terminate the pregnancy at least prior to term when the heart rate is lower than 200/min in the absence of other signs of fetal distress. Irrespective of a good condition immediately after birth, the infants with continuing tachycardia may develop overt heart failure within hours or days requiring immediate pediatric attention. Delivery of babies with IT should therefore be performed where intensive neonatal care is available.

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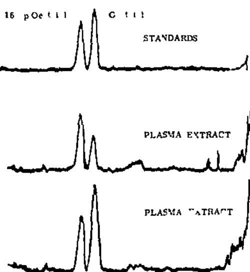


Fig 1

oestnol were plotted and the results gave a straight line passin, through the ongin (Fig 2) Monitoring of the m/e 50+ ion of oestriol trimethylsilyl ether gave a greater re sponse than 16-epi oestriol for a given weight

Reproducibility

In order to investigate the reproducibility two maternal serum samples were analysed five times The results ined (μg/100 ml) were as follows *Sample 1* 10 6 1 9 9 10 3 10 3 *Sample 2* 18 5 18 0 19 0 18 7 and The coefficient of variations was 8 3% for *Sample 1* 6 5% for *Sample 2*

Oestriol levels in maternal and umbilical cord plasma

The following results for plasma oestriol in maternal arm vein and cord vein plasma in normal and small for dates cases were obtained

	Oestriol levels (μg/100 ml)	
	Normal	Small for dates
Number of patients	40	15
Mean maternal plasma oestriol	12 7 ± 5	10 8± 2 9
Mean cord vein plasma oestriol	123 37±37	97 0±24 0

Determination of oestriol levels in scalp blood

In the series of normal and small for-dates patients fetal scalp capillary blood was taken for determination of pH It was considered of interest to monitor the oestriol concen tration in pooled samples of this blood remaining after the pH estimation It was impractical to determine oestriol in individual samples and the determination was carried out in duplicate on two separate pools obtained from the nor mal and small for dates groups of cases The oestrogens

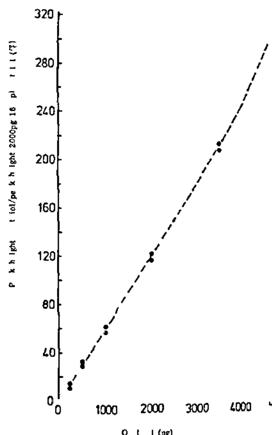


Fig 2 Relative response of oestriol to 16-epioestriol the range 0–5000 PG

were extracted from whole blood (? ml) by sonic twice with 5 ml acetone ethanol 1 1 for 30 min t ethyl acetate extracts were dried and the steroid conju gates hydrolysed in similar fashion to umbilical cord v plasma

The mean amount of oestriol present in the samples of normal scalp capillary blood was 180 μg/100 ml and in small for-dates 165 μg/100 ml If it is assumed that plasma accounts for half the volume of whole b then the mean concentration of oestriol in fetal scalp plasma for our series is about 90 μg/100 ml in normal cases and 82 5 μg/100 ml for small for-dates cases

DISCUSSION

In the clinical care of women during pregnancy there is extensive literature to show that serial esti mates of oestriol are a valuable guide to placental function and fetal wellbeing In this respect close attention has been given to lowering perinatal mor tality and morbidity in common pregnancy compli cations such as pre eclampsia (7 8 16) and retarded fetal growth and development (3 21) Active treat ment by intermittent abdominal decompression was

roduced for pre eclampsia (5) and for small for tes cases (11) with improvement in placental rmone metabolism and fetal mortality rates con med by later work (12 13) and by the additional e of sonar increase in fetal growth and viability as shown to occur (20)

Estimation of oestriol has in the past been made on 24-hour urine collections but parallel values ve been reported for plasma specimens and the e of radioimmunoassay described (10) and the ad ntages of this method evaluated both in normal d abnormal pregnancy (9 14)

In the present study with a view to learning more out the distribution of oestriol we investigated its vels in the maternal peripheral vein the fetal scalp d the baby s cord We found that the mean estriol values for maternal plasma during the sec nd stage of labour and cord plasma at birth were oth lower in small for-dates cases compared with ormal cases The mean cord plasma oestriol at 3 37±37 μg/100 ml for normal cases compares ell with a level of 129±44 μg/100 ml previously ported (1) but Roy (15) recorded lower levels We so found that the mean oestriol concentration in ord blood was ten times that in the relative mater al blood specimens for both normal and small r-dates cases in Roy s series there was a similar n fold increase in concentration in the baby s cord ecimens compared with the levels in the mother nd Shearman and co-workers (17) reported that the mbilical vein oestriol levels were significantly gher than in the relative maternal plasma As re ds fetal capillary scalp blood just before deliv) it was found that there was a higher concentra n of oestriol in normal compared with cases of all for-dates but this was not significant Most of e recent determinations of plasma oestriol have en as mentioned carried out by saturation alysis but the potential use of gas chromato phy–mass spectrometry is now being investi ed Adlercreutz and associates (2) have demon ated the use of mass fragmentography for the ultaneous measurement of several pregnancy strogens in plasma bile and urine during preg ancy Taylor & Shackleton (18 19) have employed s technique for the identification of new oestriols is technique may be available only in specialised laboratories and its routine use is at present more pensive and time consuming than radioim assay methods as twenty minutes were re red for each chromatographic run Mass fragmentography does however offer an accurate and reproducible method for plasma oestriol assays and has the advantage in its high specificity and ease of adaptation to determine simultaneously a variety of compounds Only those compounds with a MW of 504 can interfere with the assay and since other oestriols are present only in small amounts they do not constitute a problem It was further shown that use of an oestriol epimer as internal standard results in good reproducibility of assay and a correction for procedural losses No correc tion was possible for variation in the efficiency of hydrolysis but the technique used was described and validated by Corker & Naftolin (6) from whom stems the recent use of oestriol plasma analysis by radioimmunoassay methods

Recently other communications on the mass spectrometric analysis of oestrogens have been published Adlercreutz and colleagues (2) de veloped a mass fragmentographic method for the simultaneous determination of several oestrogens in plasma bile and urine of pregnant women The internal standards used were oestrogentri methylsilyl ethers prepared with deuterium la belled reagents which were added to the sample im mediately prior to gas chromatographic mass spectrometric analysis No correction was there fore possible for losses occurring during oestrogen extraction from the body fluids GC MS techniques have been shown to be particularly useful for vali dation of routine methods of oestrogen analysis Bjorkem and his co workers (4) measured urinary oestriol by mass fragmentography using an internal standard of (2 4^2H_2) oestriol and compared the results to their routine laboratory method based on a Kober reaction and also to a gas chromatographic method A good correlation was obtained between all three techniques Undoubtedly mass frag mentography will be increasingly used for vali dation of routine steroid determinations Several new urinary oestriol and oestriol one epimers have recently been identified by GC MS in this labora tory (18 19) and present research is directed to the measurement of these steroids by selected ion recording in normal and abnormal pregnancies

ACKNOWLEDGEMENT

We wish to thank Miss S M Bekhit FRCS MRCOG for her help in the collection of the various specimens

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Submitted for publication Aug 7 1977

M P Willmott
Northwick Park Hospital
Harrow Middlesex
England

Acta Obstet Gynecol Scand 57 415–419 1978

PREOPERATIVE CERVICAL MICROBIAL FLORA AND POST ABORTION INFECTION

P J Moberg [1] P Eneroth [2] J Harlin [2]
Åsa Ljung[3] and C E Nord[4]

From the [1]Department of Obstetrics and Gynecology the [2]Hormone Laboratory of the Department of Obstetrics and Gynecology the [3]Department of Clinical Microbiology Karolinska Sjukhuset Stockholm and the [4]National Bacteriological Laboratory Stockholm Sweden

Abstract With the aim to find criteria for the prediction of the patients who are at risk of developing a post abortion infection the pretreatment cervical microbial flora was compared between one series of patients who developed and another series of patients who did not develop such an infection. Aerobic and anaerobic bacteria as well as mycoplasma and fungi were studied in 104 patients The distribution of aerobic and anaerobic bacteria was similar in the 14 patients who later developed post abortal infection and in uncomplicated cases It is concluded that the observation of the cervical microbial flora cannot serve as a basis for the prediction of which patients will develop subsequent genital infections

One of the important complications of first trimester abortion by vacuum aspiration (VA) is pelvic infection (1 5 7 11 16) The incidence of this complication varies (1 5 16) widely (0 3–18%) due to differences in 1) definitions of post abortion infection 2) use of prophylactic antibiotic treatment and 3) time of observation

Few reports on infection complicating VA have dealt with the factors which might have had an influence on the occurrence of pelvic infection after abortion (1 13) In some reports on the normal microbial flora of the cervix it has been pointed out that the cervix can be a reservoir of potentially pathogenic microorganisms (9 17) which have been regarded as normal contaminants However it has been postulated that these microorganisms do not cause symptoms under normal conditions (10 17) It has also been indicated that the microorganisms which predominate in female genital tract infections reflect the normal vaginal flora The cervix is believed to be the portal of entry (3 8 22)

In an attempt to predict those patients who would develop a post abortion infection a prospective study was performed The cervical microbial flora—including aerobic and anaerobic bacteria as well as mycoplasma and fungi—was studied immediately before the abortion No prophylactic antibiotics were administered The initial microbial flora of the patients who developed post abortion infection was compared to that of the uncomplicated cases If the cervical microbial flora is an important factor in the subsequent development of infection after the abortion it would be expected to be different in the two groups

MATERIALS AND METHODS

The patients were 104 healthy women aged 14–42 (Table I) who underwent abortion in the first trimester The gestation was calculated from the first day of the last menstrual period (Table II) At a general examination 2–10 days prior to operation none of the patients reported receiving antibiotic therapy during the previous month No signs of genital infection requiring local therapy was revealed Specimens for cultivation of N gonorrhoeae were taken

Operation was performed on an outpatient basis Specimens for aerobic and anaerobic bacterial cultivation were taken by inserting dry charcoaled cotton swabs 10–1? mm into the cervix One swab was put into Stuart s modified transport medium and brought to the Dept of Clinical Microbiology Karolinska Hospital The second one was put into Shepards U9 broth with penicillin (18) and was kept at +4°C during the transportation to the Dept of Clinical Microbiology Uppsala where cultivation and identification of T mycoplasma was performed The vagina was cleansed with 0 05% aqueous chlorhexidon (ACO Sweden) Paracervical block was followed by dilatation with Hegar dilators After 5 IU of Oxytocin had been administered intravenously vacuum aspiration was performed with a metal cannula A check curretage with a blunt currette was carried out in all cases No immediate postoperative complications occurred

All patients were observed at the hospital for 5 hours following the operation They were instructed to contact

Table I *Distribution of patients according to age*

Age	N
-14	1
15-19	19
20-24	16
25-29	37
30-34	20
35-39	8
40-	3
Total	104

the hospital in case of pelvic pain temperature rise to 38 0°C or above foul vaginal discharge or blood loss exceeding an ordinary menstruation The observation time was two months

The swab in Stuart s modified transport medium was cultivated within two hours on the following media one blood agar plate (Columbia agar BBI Cockeysville Md USA with 5% horse blood) one agar plate containing 3 55% phenylethanol agar (Difco Detroit Michigan USA) one Endo agar plate (Difco) all of which were incubated aerobically for 24 h at 37 C one blood agar plate containing 0 01% gentian violet which was incubated anaerobically in a Gas Pak jar (BBL) for 24 h at 37 C one haematin agar plate (BBL) which was incubated for 24 h in 10% carbon dioxide athmosphere at 37°C and one freshly prepared blood agar plate which was incubated anaerobically for 48 h at 37 C This plate was kept for 5 days to allow appearance of B melaninogenicus Finally the swab was inserted in dextrose serum broth and thioglycollate broth and incubated for 24 h at 37 C before microscopic examination

Identification of the aerobic and anaerobic bacteria was made according to Cowan & Steel and Holdeman & More (4 12) Coagulase negative staphylococci were typed to the species level according to the scheme of Kloos & Schleifer (14) Coagulasepositive staphylococci were phage typed (7) Typing of isolated fungi was performed at the National Bacteriological Laboratory

RESULTS

Out of the 104 patients who had an abortion 89 had no signs of infection during the two months following the operation Fifteen patients contacted the hospital because of discomforting gynecological symptoms One of these patients had no objective symptoms and received no treatment Seven of the patients were treated with antibiotics on an outpatient basis due to symptoms of a mild or suspected uterine and/or adnexal infection which made them seek advice at the hospital three days to six weeks after the abortion Seven of the patients were hospitalized upon judgement by the gynecologist on duty because of an endometritis salpingitis and were treated with amoxycillin and/or doxycyclin in adequate doses In six of these patients th diagnosis was clear and was confirmed by a consultant gynecologist The diagnosis of adnexal infection could not be confirmed in one of th hospitalized patients Five of the hospitalized patients with an obvious gynecological infection wer admitted within 48 hours after the operation On patient with an obvious gynecological infection wa hospitalized 15 days after the operation

Relevant clinical data are presented in Table III The patients have been divided into three group 1) women with no complications 2) women wit mild or suspected genital infection (patients 1-7 and 3) women with clear genital infection (patient 8-14)

The initial cervical aerobic and facultativel anaerobic bacterial flora is presented separately f each group of patients in Table IV Seventeen p tients had a positive fungal growth and 5 patient had a positive Mycoplasma culture The finding were evenly scattered among the three group Most patients had a polymicrobial flora Th number of cultures with strictly anaerobic growt was similar in the three groups as seen in Table V

DISCUSSION

The reported frequency of genital infections com plicating first trimester abortions by VA vari widely (11) Beric et al (1) and Jurukowski & Sukarov (13) presented a low occurrence of po abortion infections 0 3% and 1 3% respectively These authors reported regular prophylactic use o antibiotics or sulfonamides Stallworthy et al (2 reported a 15% incidence of pyrexia 38 C or mor for 24 hours or longer and an incidence of 3 5 for pelvic inflammatory disease septicaemia o peritonitis Moberg et al (16) reported a post abo

Table II *Distribution of patients according to gestational age*

Gestational week	N
7	4
8	0
9	39
10	30
11	8
12	3
Total	104

ble III Clinical data and microbial findings in patients with postabortal infection

° outpatient treatment H=hospitalization

...nt	Gest week	Interval abortion–admittence	Diagnosis	Treatment	Microbial findings in the cervix at the abortion
(BL)	9	6 weeks	Salpingitis	Ampicillin OP	Strept intermed Eubact lentum Lact fermentum
(AE)	10	3 days	Endometritis Salpingitis	Doxycycline Amoxicillin OP	Strept faecalis Torulopsis glabrata
(LH)	8	15 days	Susp endometritis	Erythromycin OP	Bact pneumosintes Strept sanguis
(EG)	8	3 days	Endometritis	Doxycycline Amoxicillin OP	Strept intermedius Strept mitior
(K)	8	6 weeks	Susp endometritis	Erythromycin Doxycycline OP	Staph hominis Strept durans
(B-C)	10	6 days	Endometritis	Doxycycline Amoxicillin OP	Lact buchneri
(J)	9	15 days	Susp endometritis	Amoxicillin OP	No growth
(B)	9	? days	Endometritis	Amoxicillin H	Staph saprophyticus
(Q)	10	2 days	Endometritis	Amoxicillin Doxycycline H	Strept sanguis
(S)	7	2 days	Endometritis	Amoxicillin Doxycycline H	Staph haemolyticus Strept durans
(L-43	11	1 day	Endometritis Parametritis	Amoxicillin H	Lact fermentum
(L 57	9	1 day	Endometritis Parametritis	Amoxicillin Doxycycline H	Peptococcus magnus
(G)	10	15 days	Endometritis Parametritis	Amoxicillin H	Lact buchneri
(J)	9	6 days	Susp endometritis Parametritis	Amoxicillin H	Staph epidermidis Strept agalactie Srept intermedius
(M)	10	5 days	No infection	None	Bact pneumosintes

...on infection rate of 7 2% in 1 123 patients ... 1971 The figure included early as well as late ...al abortion infections Although the reported fig...s for infection vary due to a heterogenous post...ortal infection concept based on both subjective ...ptoms and objective signs (16) the figures are ...our opinion unacceptably high

The aim of the present study was to select the ...p of patients at risk of developing a post abortion infection If the occurrence of a postabortal infection was clearly related to microbial pathogens present in the cervix it should be possible to identify these patients prior to the operation In several reports of female upper genital tract infections anaerobic bacteria are the predominating organisms in a polymicrobial flora (3 21)

The normal flora of the cervix is also ... m... plex polymicrobial composition (9 1 ... re...

Acta Obstet Gynecol Scand 57 421–428 1978

TREATMENT OF PRIMARY DYSMENORRHEA WITH PROSTAGLANDIN SYNTHETASE INHIBITORS—A PROMISING THERAPEUTIC ALTERNATIVE

Viveca Lundstrom

From the Department of Obstetrics and Gynecology Karolinska Institute Stockholm Sweden

bstract Three groups of patients with primary dys menorrhea were treated with prostaglandin synthetase nhibitors Thirty-one women received indomethacin at a se of 25 mg × 3–4 per day usually starting one to two ys before the onset of menstruation and 38 women ceived naproxen 250 mg × 3–4 per day usually starting the first day of bleeding (open studies) Seventy-one er cent of the patients experienced moderate or good ef of pain following indomethacin and 67% following proxen In a third series a double blind crossover study ing the sodium salt of naproxen versus placebo in 26 tients showed that naproxen sodium was significantly ore effective than the placebo ($p<0.05$) At the doses oyed the prostaglandin synthetase inhibitors were ot associated with any side effects of major concern The dy indicates that this form of therapy offers an effective ernative in patients who for some reasons do not accept monal treatment

ysmenorrhea represents one of the commonest mplaints in gynecological office practice The so- l handicap that this disorder imposes upon g working women students and professionals onsiderable

Combined oral contraceptives or dehydro-retro- gesterone offer efficient relief in a number of ses There is however a significant segment of female population who neither accept nor toler steroid medication The value of narcotic anal sics and/or sedatives is limited and these agents potentially dangerous

A therapeutic alternative is urgently needed taglandin (PG) synthetase inhibitors have ved to be successful in many cases of in acitating dysmenorrhea but so far few well con lled studies are available on their clinical useful ss in this condition

In this series of clinical trials we investigated the e of prostaglandin synthetase inhibitors in the tment of dysmenorrhea We proceeded in sev l steps First in an open trial we investigated the therapeutic efficacy of a traditional PG synthe tase inhibitor—indomethacin thereafter we used a novel compound with prostaglandin inhibitory properties—naproxen (20) again in an open trial Subsequently of the strong placebo effects of any medication in dysmenorrhea we designed a *double blind crossover trial* using the sodium salt of naproxen (naproxen Na)

Several other aspects of the therapeutic efficacy of PG synthetase inhibitors were studied Firstly we wanted to learn whether starting the treatment several days before the onset of bleeding would eliminate the pain more effectively than starting the treatment with the beginning of the menstrual flow This question arose in association with studies demonstrating that indomethacin decreased urinary prostaglandin metabolites by 85% after two days of administration (9) Secondly a causative rela tionship has been suggested between gastrointesti nal symptoms of dysmenorrhea and high concentra tions of circulating endogenous PGs we questioned therefore whether dysmenorrheic patients suffer ing from such symptoms may be particularly suited for treatment with PG synthetase inhibitors Another clinically important problem was whether dysmenorrhea in women who did not obtain relief with the administration of combined oral contracep- tives would respond to PG synthetase inhibitors

Finally we investigated the effects of naproxen Na on the uterine contractions and tried to define the relationship between pain relief and the decrease of uterine tonus

MATERIAL AND METHODS

Selection of patients

Women suffering from dysmenorrhea were referred to t outpatient clinic of the Department of !

Karolinska Hospital and to a community hospital in the vicinity of Stockholm There they were interviewed and examined by the investigator

Prior to admission to the study a thorough history of the menstrual distress was obtained apart from uterine cramps other symptoms associated with dysmenorrhea were recorded such as nausea vomiting diarrhea headache fever and shivering The pain relief obtained with combined oral contraceptives or analgesics was also noted Thereafter the subjects received a complete pelvic examination Only women with normal gynecological findings and who required analgesics regularly (moderate dysmenorrhea=degree 2) or who had to refrain from work (severe dysmenorrhea=degree 3) were selected for the study Women with dysmenorrhea associated with other pathological disorders such as chronic salpingitis or endometriosis were excluded from the trial One patient who had a bicornuate uterus was accepted Patients who expressed a desire for oral contraceptives were excluded No attempt was made to evaluate possible psychological factors associated with dysmenorrhea

Study groups and treatment schedules

Three main groups and one additional special group of patients constituted the trial

Group 1 included 31 patients treated with indomethacin (Indomee® Merck Sharpe and Dome) during two cycles Dysmenorrhea in 13 patients was classified as moderate (degree 2) and in 18 as severe (degree 3) Fourteen patients indicated gastrointestinal symptoms associated with menstrual cramping

The patients were recommended to take indomethacin in an oral dose of 25 mg three to four times daily starting one to two days before the expected menstruation and to continue until the pain normally would have disappeared In case a pregnancy was planned patients were recommended not to start the treatment until the beginning of the menstrual flow Twenty two patients started the treatment before the onset of the bleeding and nine on the first day of bleeding

Group 2 Thirty nine patients were selected for the treatment with naproxen (Naprosyn® naproxen (d 2 (6-methoxy 2 napthyl propionic acid) and naproxen sodium kindly supplied by Syntex Research) during three cycles Dysmenorrhea in nine patients was classified as moderate (degree 2) and in 30 as severe (degree 3) A history of gastrointestinal symptoms associated with dysmenorrhea was indicated by 18 patients

The patients were recommended to take naproxen in a dose of 250 mg twice daily starting one to two days before the expected menstruation and increase the dosage to ?50 mg three to four times daily during the days of the actual menstrual flow If the treatment proved ineffective when starting one to two days before menstruation patients were recommended to start four to five days before the expected bleeding Eleven patients succeeded in starting the medication before the onset of bleeding while 28 started during the first day of the menstrual flow

Group 3 Twenty-eight patients were selected for the *double blind crossover study with naproxen sodium versus placebo* Dysmenorrhea in ?0 patients was classified as severe (degree 3) and in 8 as moderate (degree ?) Twenty patients indicated a history of gastrointestinal symptoms associated with dysmenorrhea

On admission to the trial the patients were asked by t[he] investigator to compare two analgesics for menstr[ual] pain during a six month period using each compou[nd] successively over a three month period The patients we[re] instructed to start the study medication on the first da[y of] menstruation Naproxen Na was to be taken in a dose [of] 550 mg (? tablets each 275 mg) followed by ?75 mg eve[ry] six hours to a maximum daily dose of 1 100 mg The sa[me] number of tablets with identical physical properties w[as] prescribed for the placebo treatment The assignment [of] patients to the naproxen Na or to the placebo treatme[nt] and the sequence in which patients received the stu[dy] drugs proceeded according to a randomization schedul[e] For each treatment month on special forms the patien[ts] indicated the degree of menstrual pain gastrointestin[al] symptoms the amount of bleeding effect of the treatmen[t] and side effects After three months the patients wer[e] interviewed by the investigator and medication w[as] handed out to them for another three month period

Moreover in this group hemoglobin concentration leucocyte and thrombocyte counts as well as hepatic func[tion] tests were analyzed before the start of medication an[d] after three and six months of treatment

The patient characteristics of the three treatmen[t] groups are summarized in Table I indicating the number o[f] patients their age parity and character of dysmenorrhe[a] (historical presence of gastrointestinal discomfort fam[ily] incidence of dysmenorrhea and the degree of dys[-] menorrheic pain)

The trials included an additional *special group* co[n]sisting of three patients with dysmenorrhea and two non[-] dysmenorrheic women In these women the uterine con[-] tractility was investigated after a single oral dose of 5? mg of naproxen Na Uterine contractions were recorde[d] by means of an immobilized micro-balloon which wa[s] introduced into the uterine cavity and connected through [a] pressure sensor to a recording device (13)

Evaluation of treatment effects

After each treatment course the patients completed spe[-] cial forms indicating the degree of menstrual pain th[e] intensity of bleeding the presence of gastrointestin[al] symptoms the relief achieved by the study drug and sid[e] effects At an interview the investigator evaluated eac[h] patient s regularity of drug intake the changes i[n] dysmenorrheic symptomatology and in the menstrual flow pattern

The relief achieved by the study medication was score[d] according to the following system

0 No improvement
1 Moderate improvement (still pain but less severe than normally)
2 Marked improvement (slight pain present occasionally)
3 Complete relief

In the first overall analysis the effectiveness of the study drug was assessed by the percentage of women achieving marked improvement (scores ? to 3) and moderate improvement (score 1) as compared with the percentage of

ble I *Characteristics of patients in the different treatment groups*

reatment	No of pats	Mean years of age ± S D	Nulli para	Multi para	Gastro-intestinal discomfort	Family incidence of dysmenorrhea	Degree of dysmenorrheic pain[b]	
							2	3
ndomethacin	31	27 9±7 0 (16–41)	24	7	14	15	13	18
Naproxen	39	23 4±8 0 (13–47)	32	7	18	17	9	30
Naproxen sodium and placebo	8	24 7±8 0 (16–4?)	26	-	18	16	6	20
Total	98		82	16	50	48	28	68

Dysmenorrhea present in mothers and/or sisters of patients

moderate dysmenorrhea i e requiring regular use of analgesics 3=severe dysmenorrhea i e causing loss of working or school days

...men whose dysmenorrheic pain remained unchanged the analysis of the double blind crossover study (group 3), scores achieved during individual treatment courses were summed for the three months placebo period The statistical methods employed in analysis are described in the Results section below

In the special group where uterine contractions were recorded the time to reduce uterine activity and its maximum reduction following a dose of 550 mg of naproxen Na were recorded and correlated with pain relief times

RESULTS

Analysis of the different treatment groups

The overall results of the three groups studied are presented in Table II with pain relief side effects and changes in menstrual pattern recorded numerically

Group 1 Indomethacin

Among the 31 patients who were treated with indomethacin there was complete relief or marked decrease in pain in 20 (65%) and a moderate effect in two (6%) The treatment was ineffective in 29% ... patients reported side effects probably induced by the drug namely four cases of headache ... of exanthema one of nausea and one of severe ...itus which forced the patient to stop the treatment immediately Decreased bleeding was observed by two patients increased bleeding by one and there was a delay of menses of 5–7 days in ...o subjects

Group 2 Naproxen

...9 cases treated with naproxen good pain relief ... experienced by 23 subjects (59%) while three ... had moderate relief No improvement was ...d in 33% Side effects probably due to medication occurred in three patients headache in two cases and fatigue in one Decreased or shortened menstrual flow was observed by ten subjects increased bleeding by two and delay of menstruation by a further two

Group 3 The double blind crossover trial with naproxen Na

(a) The overall effect of the study drugs Twenty eight patients started the first three month period of the study 14 on naproxen Na and 14 on placebo However only 26 patients (two patients became pregnant after the first three months of treatment) crossed over and started the second three month period (13 on naproxen Na and 13 on placebo) As shown in Table II naproxen Na 22 patients (85%) experienced marked or moderate improvement and four (15%) no improvement The corresponding figures for the placebo treatment period were 9 patients with marked to moderate improvement (34%) and 17 patients no improvement (65 %) There was no significant difference between the two groups with regard to the incidence of side effects in one patient the rash following naproxen Na could have been ascribed to the compound

Menstrual disorders were recorded in eight cases of the naproxen Na group but in only four patients of the placebo group In one patient of the former group the duration of menstrual flow decreased from six days to only one day and this was accompanied by complete relief of the pain of her otherwise incapacitating dysmenorrhea

(b) The crossover analysis The effect of naproxen Na in the treatment of dysmenorrhea compared with a placebo is illustrated in Fig 1 Each patient is presented individually and irrespective of the treatment order The effective

Table II *Pain relieving effect side effects and change in menstrual bleeding in the different treatment grou*

Treatment	No of pats	Marked improvement (scores 2–3) No	%	Moderate improvement (score 1) No	%	No improvement No	%	Side effects No	%
Indomethacin 25 mg × 3–4	31	20	65	2	6	9	29	7	23
Naproxen 250 mg × 2–4	39	23	59	3	8	13	33	3[b]	8
Naproxen sodium 550 mg + 275 mg + 275 mg	26	13	50	9	35	4	15	4	15
Placebo	26	4	15	5	19	17	65	5[d]	19

Indomethacin headache 4 gastritis 1 nausea 1 exanthema 1
[b] Naproxen headache 2 fatigue 1
Naproxen sodium headache 2 fatigue 1 exanthema 1
[d] Placebo depression 2 headache 1 fatigue 1 dizziness 1

treatment was evaluated once a month and the horizontal bars represent the sum of the scores obtained during each three month period either on naproxen Na or placebo Individual exceptions aside it seems evident that the scores for naproxen Na treatment were superior to those of placebo Only four patients evaluated the placebo tablets higher than the active drug whereas twenty preferred naproxen Na

The statistical method employed in the crossover analysis was the Wilcoxon signed rank test Patients who completed only one treatment course on placebo or on naproxen Na (in Fig 1 pointed out by asterisks) were excluded from analysis Thus 22 patients could be evaluated 10 in the naproxen Na→placebo sequence and 12 in the placebo→naproxen Na sequence The analysis of the individual differences in scores between the naproxen Na period and the placebo period revealed a significant difference in favour of naproxen Na with a p value of 0 035

(c) Parallel analysis Parallel analysis for the first three month period only was performed as well The therapeutic effects of naproxen Na in 14 patients was compared with the effect achieved by placebo in the other 14 The Wilcoxon two sample test yielded a p value of 0 024 in favour of naproxen Na

(d) Laboratory tests No abnormal changes in hemoglobin leucocyte count and hepatic function tests were observed after treatment with either naproxen Na or placebo One patient treated with naproxen Na showed a drop in thrombocyte count from 250 to 80 thousand/mm³ After two cycles the values were 222 again However a similar drop was also observed in three placebo cases 2/6 to 130 315 to 160 and 200 to 135 these may indicate spontaneous variations or erroneous counting by the routine laboratory

Initiation of therapy in relation to the commencement of menstrual flow

Table III represents an analysis of the pain relieving effect of indomethacin and naproxen with regard to the day of the cycle on which the treatment was started

Patients who obtained PG synthetase inhibitors 1–5 days before the onset of their menstrual flow were compared with those treated from the first day of bleeding The overall results indicate that there was no difference in pain relief between these two modes of administration

However the present case material also included exceptional cases where the duration of PG synthetase inhibitor treatment premenstrually did seem to be of importance for the alleviation of dysmenorrheic pain

One patient a 17 year old nulligravida with dysmenorrhea since the age of 12 had suffered from severe pain and frequent vomiting to the extent that she had to stay in bed for one to two days every month She did not experience any relief with indomethacin 50 mg rectally twice a day one day prior to menstruation nor with naproxen orally at a dose of 250 mg three times daily starting two days before expected menstruation However when naproxen medication was begun 5–6 days before menses there was complete relief of pain as well as of all her gastrointestinal symptoms This effect was observed during three different cycles

sed rged g	Decreased or shortened bleeding		Delay of menses	
%	No	%	No	%
1	?	6	2	6
5	10	6	2	5
4	6	23	1	4
4	3	17	0	–

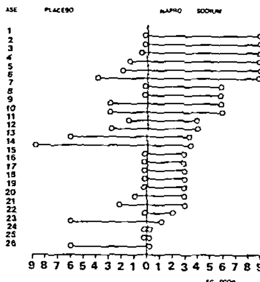


Fig 1 Diagram illustrating the results of a double blind crossover study of naproxen sodium versus placebo in the treatment of dysmenorrhea The horizontal bars on each side of the vertical line represent the sum of pain relief scores during three cycles

Gastrointestinal symptoms

Nausea vomiting and diarrhea occurred in about 50% of the dysmenorrheic women It was interesting to note that women who experienced a significant relief of uterine pain by PG synthetase inhibitors also experienced a disappearance of their gastrointestinal disturbances Table IV represents a separate analysis of patients with and without gastrointestinal symptoms (vomiting and/or diarrhea) accompanying the period of menstrual pain However the pain relieving effect of PG synthetase inhibitors did not differ significantly between these categories of patients

Oral contraceptives

Seven women suffered from dysmenorrhea in spite of the fact that they had been using combined oral contraceptives These women represent a cross section from all three groups When treated with PG synthetase inhibitors eight experienced complete relief or marked improvement of their symptoms

The effect of naproxen Na on uterine contractility

As illustrated in Fig 2 naproxen Na exerted a relatively prompt effect on uterine contractility in the small group of five patients The spastic and hypertonic contractility pattern of the uterus in cases of dysmenorrhea was altered within a period of approximately one hour to attain contractions of significantly lower amplitudes lower frequency and lower basal tone This change in contractility was followed by complete disappearance of pain in all three dysmenorrheic women in whom the uterine activity was registered This suggested a very rapid action of the orally administered naproxen Na A similarly rapid change in uterine contractility was also observed in the two women not suffering from dysmenorrhea

DISCUSSION

The first report on the use of anti inflammatory drugs for the treatment of dysmenorrhea appeared in 1953 Fox (7) observed that women treated with phenylbutazone for rheumatic conditions experienced a decrease in their menstrual pain and discomfort Twenty years later Hill (11) and Christensen (3) reported that indomethacin had a favourable analgesic effect in women with dysmenorrhea Apparently none of these authors were aware of the probable mechanism of action of such anti inflammatory drugs namely that of the inhibition of prostaglandin synthesis Layes Molla & Donald (16) who compared the effect of ibuprofen and paracetamol in a double blind study of dysmenorrheic women might not have recognized the significance of this mechanism since neither prostaglandins nor prostaglandin synthetase inhibitors were mentioned in their paper The reported complete relief or improvement of symptoms in 62–64% of their cases in the two groups

Table III *Pain relieving effect of indomethacin or naproxen when starting medication before or at the beginning of menstruation*

Groups I and II	No of pats	Marked improvement		Moderate improvement		No improvement	
		No	%	No	%	No	%
Patients starting medication before onset of menses	33	20	61	2	6	11	33
Patients starting medication at the beginning of menses	37	26	70	2	5	9	[illegible]

Vane's (1971) experimental studies on the mechanism of action of aspirin and indomethacin created a sound basis for the understanding of the beneficial effects of these drugs on dysmenorrhea (21). With this discovery in mind Schwartz et al (19) conducted the first clinical study of the effect of flufenamic acid in cases of dysmenorrhea. The trial comprised 16 patients who took flufenamic acid orally during a total of 31 cycles. The drug abolished the symptoms in all patients. The same group of women obtained analgesics, spasmolytics, tranquillizers or placebo over 72 cycles, but these afforded no significant relief. Similarly Massey et al postulated that the analgesic effect of naproxen in uterine pain following IUD insertion was due to the prostaglandin inhibitory effect of this compound (16).

The correlation between high uterine tonus and dysmenorrheic pain has been suggested by several authors (1, 4, 5, 6). In an earlier study Lundstrom et al (13) established that oral and rectal administration of indomethacin decreased the uterine tonus as well as the amplitude and frequency of the contractions in dysmenorrheic women and that these alterations in uterine activity occurred simultaneously with the relief of pain.

Csapo et al (5) and Lundstrom & Gréen (14) made the same observations using naproxen Na. The latter authors also showed that at the beginning of menstruation the concentration of $PGF_{2\alpha}$, as determined by gas chromatography mass spectrometry, was higher in the endometrium of dysmenorrheic women than in non-dysmenorrheic subjects.

Boehm & Sarratt (2) reported the results of an open clinical study where 83% of 30 women experienced pain relief by taking indomethacin (50 mg three times a day). A clinical double blind study of the effect of PG synthetase inhibitors in the treatment of dysmenorrhea by Henzl et al (12) showed that naproxen Na had a significant pain relieving effect.

The case material in the present study was divided into three groups of which groups I and II may be characterized as common open studies. Seventy one per cent of the patients in the indomethacin series and 67% of the naproxen treated patients obtained complete or partial relief from their pain. These results are approximately the same as those achieved by other investigators.

Dysmenorrhea is a multifactorial syndrome where psychological influences may play a role. Moreover cycle irregularities as well as the difficulty of measuring pain and the degree of pain relief create problems in the objective evaluation of the results. A carefully controlled double blind study r

Table IV *Correlation between gastrointestinal symptoms and pain relieving effect*

Condition	Number	Marked improvement		Moderate improvement		No improvement	
		No	%	No	%	No	%
Dysmenorrhea with gastrointestinal symptoms	50	31	62	7	14	1	[illegible]
Dysmenorrhea without gastrointestinal symptoms	46	28	61	33	7	15	33

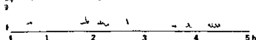


Fig 2 Recording of uterine contractility in a woman suffering from severe menstrual pain (day 2 of menses) One hour after oral administration of naproxen sodium reduction of uterine tonus and frequency and amplitude of contractions is seen Simultaneously with the decrease in uterine contractility the patient became completely free from symptoms

therefore of major importance for an evaluation of the drug effect

Although it is difficult to complete a double blind crossover study in dysmenorrheic women it is believed that this design offers a more accurate assessment of the results than simple double blind trials since the same patient experiences the effect of both the active drug and placebo

Group 3 in the present investigation participated in a double blind crossover study The results showed that the symptoms of 85 % of the volunteers in the naproxen Na group were completely or partially improved compared with 34 % of the placebo group The PG synthetase inhibitor effect is similar to that found by most other authors while the placebo effect corresponds to expected levels

If the degree of pain is difficult to assess it is even more difficult to define and evaluate the occurrence of different drug induced side effects This is illustrated by the fact that the placebo group had a higher incidence of side effects than the active drug treatments of both groups 2 and 3 Although the indomethacin group had the highest overall rate of side effects of all three groups definite conclusions in this respect cannot be made However the only severe side effect that occurred in the series was one instance of marked gastritis and this case belonged to the indomethacin group Boehm & Sarratt (3) reported a comparatively high incidence of side effects with indomethacin but they used twice the dose employed in this study Differences between the groups with regard to changes in menstrual flow were difficult to assess It should however be emphasized that there was a tendency towards a decrease in the duration of menstruation under PG synthetase inhibitor treatment

An observation that may be of some clinical interest is that patients with both dysmenorrhea and gastrointestinal symptoms namely diarrhea and vomiting (which are well known side effects of PG administration) responded no more favourably than those without gastrointestinal symptoms Analysis of the timing of medication indicated that the pain relieving effect was the same whether medication was started before expected menstruation or on the first day of menstrual bleeding Thus the fact that most patients do not have to start taking PG synthetase inhibitors until the onset of symptoms of impending menstruation has obvious practical advantage The rapid absorption of naproxen Na may be of particular significance when considering this aspect of administration In some individuals however the administration of PG synthetase inhibitors prior to menstruation is necessary and clinically beneficial

β_2 adrenergic stimulating drugs have recently been shown to inhibit uterine hypercontractility associated with dysmenorrhea (1) However these compounds do not appear to be clinically useful Terbutaline taken orally reduced menstrual pain but caused too many side effects such as tremor and tachycardia to be acceptable (1) Other studies by Hansen & Secher (10) using hydroxyphenyl orciprenalin and by Nesheim & Walloe (17) using isoxuprine showed no significant effect in the relief of dysmenorrhea when compared with a placebo

The most effective therapy for dysmenorrhea is still hormonal treatment Combined oral contraceptives which reduce pain in 95 to 98 % of the patients cause anovulatory cycles Dehydro-retroprogesterone which does not block ovulation also offers very effective pain relief in this syndrome The action of the latter compound is not clear Pickles has demonstrated in one patient that an anovulatory cycle resulted in a decrease of PGF_2 in the menstrual fluid to a fifth of the content in an ovulatory cycle (18) Lundstrom (14) has shown that oral contraceptives reduced the PGF_2 concentration by 75 % in the endometrium in one patient Whether dehydro-retro-progesterone also reduces PG synthesis has not yet been studied but a similar mechanism seems possible

CONCLUSION

Naproxen Na with its potent action on PG synthesis and rapid oral resorption combined with few side effects offers an effective therapeutic alternative in patients who do not accept hormonal therapy for the treatment of their dysmenorrhea or who do

not desire a birth control method anyway or who suffer from dysmenorrhea in spite of hormonal contraception

ACKNOWLEDGEMENT

The author is indebted to Astra Syntex Inc Sodertalje Sweden for the generous supply of the naproxen sodium and placebo tablets to Dr Jerry Johnson Syntex Research Palo Alto California for the statistical evaluation of the results and to Ms L M Lindeholm for excellent secretarial assistance My thanks are due to Professor Nils Wiqvist and Dr Milan Henzl for valuable suggestions and a careful critical review of the manuscript

The investigation was supported by the WHO Expanded Programme of Research Development and Research Training

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Submitted for publication May 2 1977

Viveca Lundstrom
Dept of Obstetrics and Gynecology
Karolinska Sjukhuset
S 104 01 Stockholm
Sweden

Acta Obstet Gynecol Scand 57 429–433 1978

RECORDING OF MYOMETRIAL ACTIVITY IN THE NON PREGNANT HUMAN UTERUS BY A MICRO TRANSDUCER CATHETER

M Åkerlund L Ph Bengtsson and U Ulmsten

From the Departments of Obstetrics and Gynaecology Lund and Malmo University of Lund Sweden

Abstract A micro-transducer catheter was tested *in vitro* and *in vivo* for recording of myometrial activity in the non-pregnant human uterus and was also compared with conventional fluid filled open end catheters previously used for recording intra uterine pressures The micro-transducer catheter had a frequency response far above that of fluid filled open end catheters It was easily introduced through the uterine cervix and was never obstructed Provided that the sensory surface of the micro-transducer was kept from direct contact with the uterine wall by some special arrangement it gave recordings of the intra-uterine pressure that were practically identical with those obtained by an open end catheter

A variety of catheters have been used for recording intra uterine pressure in non pregnant women Braaksma et al (6) made a comparison both *in vivo* and *in vitro* and found that open end (7) and sponge tipped (4) catheters gave reliable results whereas closed tipped catheter systems (membrane micro-balloon or ballontip catheters) did not

However the open end catheter often becomes obstructed at the intra uterine end by mucus blood or endometrial fragments and requires therefore repeated flushing or continuous counter pressure The spongetipped catheter also sometimes becomes obstructed but less frequently than the open end catheter Furthermore the occurrence of leakage or air bubbles in the fluid filled open end catheter may result in distorted recordings

All these functional disadvantages of fluid filled catheters might be overcome by the recently constructed micro-transducer catheter Such a catheter has until now mainly been used for recording pressure in body cavities such as the heart the large blood vessels and the female urinary tract (3 8 10 11)

The aim of the present study was to investigate whether such a micro-transducer catheter could be used for recording myometrial activity in the non pregnant uterus In the same study we also wished to compare the micro-transducer catheter with conventional fluidfilled open tip catheters previously used for recording intra uterine pressure For this comparison we chose the open end catheter in order to keep the added volume of the intra uterine part as small as possible

MATERIAL AND METHODS

Recording systems

The construction of the two different recording systems is briefly as follows

The micro-transducer catheter consists of a dacron catheter 2 31 mm outer diameter In the tip of this catheter a micro-transducer is enclosed (Millar Instr Houston Texas USA) The sensor is a silicon semiconductor unbonded strain gauge with the sensor surface at the side of the catheter tip According to the manufacturer it has the following technical data Frequency response 0 (dc)—20 kHz Internal calibration 100 mmHg±2 mmHg Range −300 to +400 mmHg Reference pressure Vent to atmosphere Hysteresis and linearity Error less than 0 5% F S

These data were confirmed by tests in the department of bio-engineering at our hospital The thermal stability given in the manufacturer s manual (±0 1 mmHg/°C at 25–40°C) did not always prove to be reliable in our tests and the experiments and calibrations were therefore always done at a constant temperature (37 °C)

The pressure transducer was connected to an amplifier (EMT 311 Elema Siemens Stockholm Sweden) and a potentiometer recorder (Omniscribe Houston Instr Texas USA)

The open end catheter recording system consists of a catheter made of vinyl the inner diameter 0 5 mm and the outer diameter 0 9 mm The length of the catheter is 1 meter The outer end of the catheter was attached to a conventional pressure transducer (EMT 35 Elema Siemens) an amplifier (EMT 311 Elema Siemens) and the potentiometer recorder

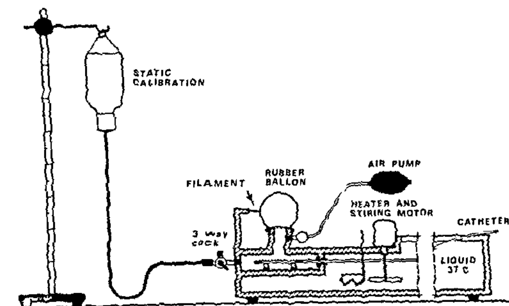


Fig 1 Cross section of the calibrating system ready for a *dynamic calibration of the micro-transducer catheter* which is inserted into the pressure chamber The dynamic calibration is performed by bursting the rubber balloon connected to the fluid filled pressure chamber The pressure within the chamber is thereby momentarily reduced to atmospheric pressure Another catheter can be introduced into the calibrator if the static calibration equipment is demounted

Experimental procedures

Studies in vitro Both recording catheters were calibrated and tested against each other in a specially designed test chamber where the pressure was regulated by a rubber balloon (Fig 1)

This test chamber or calibrator in which it is also possible to disinfect the catheters has previously been fully described (7)

Studies in vivo Twenty healthy women of fertile age who had been fully informed and had consented to the investigation were recorded in different periods of the menstrual cycle In the first series of investigations the micro-transducer catheter was inserted alone into the uterine cavity so far that the pressure sensing section of the catheter was placed in the fundus

In order to expose the sensory surface alternatively to the anterior and the posterior walls and to the mucus filled slit between the walls the catheter was turned around its axes at a constant intra uterine level

In the second series of investigations the microtransducer catheter was inserted tied to an open end catheter and a thermistor catheter (Fig 2)

This catheter has previously been used for simultaneous pressure and blood flow recording (1) As can be seen in Fig 2 the two additional catheters created a bridge over the sensory area of the micro-transducer catheter submitting it to the same pressure within the surrounding mucus as the open end catheter By this arrangement direct pressure of the uterine walls on the sensory area of the micro-transducer could be avoided

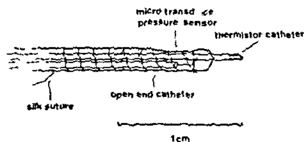


Fig 2 The pressure sensing section of a microtransducer catheter combined with a thermistor catheter and an open end catheter as they were used in the *in vivo* recordings

RESULTS

The results from the *in vitro* investigations are presented in Figs 3 and 4

From Fig 3 it is seen that the reaction time of the micro transducer catheter is <1 msec and that of the open end catheter about 80 msec The results from the dynamic tests in the test chamber are illustrated in Fig 4 As can be seen the micro-transducer and the open end catheter recordings are in all respects identical sharing the same amplitude and shape of the recorded pressure change

During the *in vivo* investigations it was found that

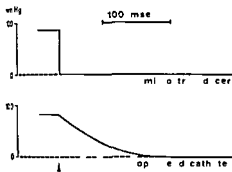


Fig 3 Reaction times of the two different recording systems tested in the calibrator At the arrow the rubber balloon is burst

the micro-transducer catheter caused almost no discomfort when introduced through the uterine cervix It functioned without interruption during all the recordings even when they lasted up to 10 hours The open end catheter on the other hand had to be flushed intermittently to function adequately When the micro-transducer catheter was used alone *in vivo* it gave in different periods of the menstrual cycle patterns of pressure changes similar to those obtained previously by open end and sponge tipped catheters However it was noticed that both amplitude and basal tonus in the recordings could sometimes be changed up to 10 mmHg when the direction of the sensory surface of the catheter tip in the uterine cavity was changed by turning the catheter around its axes When the sensory area was kept from direct contact with the uterine walls by the thermistor catheter turning of the micro-transducer catheter did not have any influence Practically identical recordings were obtained from both the micro-transducer and the open end catheter (Fig 5)

DISCUSSION

The pregnant uterus contains a fluid filled cavity In all parts of this cavity the pressure under static conditions is the same if differences due to hydrostatic pressure are overlooked It is important to stress that the normal non pregnant uterus has no real cavity but only a slit between the anterior and posterior wall filled by endometrium and a small amount of mucus This has been fully proved by experiments where 2–3 small balloon catheters (9) or 2–3 sponge tipped catheters (5) have been inserted into the uterine cavity By these means different pressures have been recorded at different levels of the cavity Thus around each catheter tip—irrespective of whether it is a small balloon sponge tipped of an open end catheter a small space is created filled by fluid The pressure which is recorded from this space is the resultant of all contractile activities in the surrounding parts of the uterine walls

The inertia or more accurately the frequency response of a fluid filled open end catheter system depends on among other things the length of the catheter its diameter the material of which it is made and the compliance of the pressure transducer Recording of intra uterine pressures is complicated by the long narrow fluid filled catheters that must be used Fig 3 indicates that the frequency response of the micro-transducer catheter is much better than that of the open end catheter It is evident from Figs 4 and 5 that the frequency response of the open end catheter under optimal conditions is sufficient to record the intra uterine

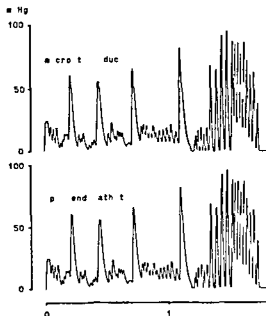


Fig 4 Comparison of pressure recordings *in vitro* by the micro-transducer catheter and the open end catheter system in the calibrator The pressure fluctuations were brought about by compressing the inflated rubber balloon by hand The recordings from the two catheter systems do not differ in any respect

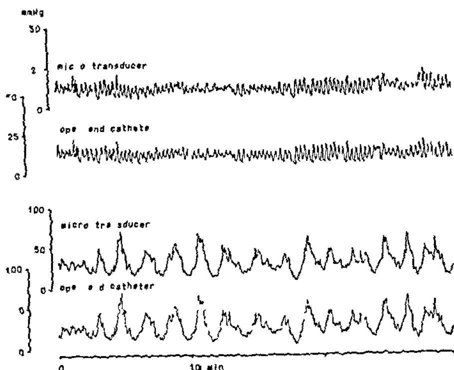


Fig 5 Comparison of simultaneous *recordings* of intra uterine pressure by a *micro-transducer and an* open end catheter The sensory surface of the microtransducer was kept from direct contact with the uterine walls by the arrangement shown in Text fig 1 The upper two tracings represent recordings from a woman on day 15 in a normal cycle of 28 days The lower two tracings are recordings from a woman on day 1 in a normal cycle of 25 days In each pair of recordings the two pressure curves are practically identical

pressure variations caused by the myometrial activity

However the frequency response of the open end catheter is easily decreased by clotting air bubbles and leakage in the recording system which can result in distorted recordings When the micro transducer is used there is no risk of such disturbances of measurement However the results of the present study suggest that in order to give recordings in all respects similar to those obtained by open end catheters the sensory surface of the micro-transducer catheter should be kept from a direct close contact with the uterine wall by some special arrangement When the micro-transducer is used with an uncovered sensory surface permitting such a close contact with the uterine wall the recordings show the same activity patterns as those obtained by other catheters but the basal tonus and the amplitude can deviate to a certain degree

From our investigations it can thus be concluded that when correctly used the micro-transducer catheter gives both reliable and reproducible recordings of the intra uterine pressure Such a recording catheter has several advantages over previous methods It is easily introduced through the uterine cervix It is never obstructed It has a frequency response far above that of fluid filled open end catheters It includes a standardised simple and reliable calibration of the whole recording system including simultaneous disinfection of the recording catheter

ACKNOWLEDGEMENT

We wish to thank Mr Lars-Goran Angantyr Department of Bio-engineering Hospital of Lund for his valuable technical advice

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Submitted for publication Oct 26 1977

Mats Åkerlund
Department of Obstetrics and Gynecology
University Hospital
Lund
Sweden

Acta Obstet Gynecol Scand 57 435–437 1978

CHANGES IN BONE MINERAL CONTENT IN WOMEN WITH NATURAL MENOPAUSE DURING TREATMENT WITH FEMALE SEX HORMONES

Nils Dalen Mirjam Furuhjelm Bertil Jacobson and Bertil Lamke

From the Department of Medical Engineering Karolinska Institutet Department of Roentgenology Karolinska Sjukhuset and Department of Obstetrics and Gynecology Sabbatsberg Sjukhus Stockholm Sweden

stract The bone mineral content was determined in ...teen women with a natural menopause by X ray ...ctrophotometry during treatment with a combination ...estrogens and a gestagen During a three year follow up ...riod the hormone treated women significantly increased ...< 0 05) their mineral content by 3% a year on average ...compared with a control group Even in patients who ...d passed the menopause several years previously the ...crease occurred and was particularly great during the ...st year of treatment

...ostmenopausal women show a greater tendency to ...actures than men of a comparable age Albright et ... (?) observed this sex difference in fracture ...pidemiology and suggested that older women de...elop osteoporosis due to decreased ovarian func...ion

Although female sex hormones have been used ...r several decades long term prospective studies ...n the effect of such treatment on the skeleton are ...w (11 12)

The present study describes the changes in bone ...ineral content found in a group of women with ...tural menopause during treatment with female ...ex hormones

MATERIAL AND METHODS

The material comprised women attending a gynaecologist ...or postmenopausal symptoms such as flushes sweating ...nervousness or for signs of atrophic vaginal and urethral ...mucosa All the patients had passed the natural ...menopause at least two years previously and were in good ...physical condition The patients were treated with a com...bination of estrogens and gestagen according to the follow...ing schedule Estradiol 4 mg+estriol 2 mg for 12 days ...followed by estradiol 4 mg + estriol 2 mg + norethisterone ...acetate 1 mg for 10 days followed by estradiol 1 ...mg+estriol 0 5 mg for 6 days Blood estrogen was esti...mated at 6 months intervals By this treatment blood estrogen was kept at the same level as in the luteal phase of a normal menstrual cycle The cyclic supplement with gestagen secured a regular shedding of the endometrium in all patients

For ethical reasons the patients were not given placebo Instead each patient was compared with a con trol of similar age A selection was made to obtain controls with postmenopausal symptoms In the original group of 14 patients 3 were excluded as treatment was interrupted The age of the hormone treated women was 56±5 years and of the controls 55±4 years (mean S D)

The bone mineral content was determined by X ray spectrophotometry (7 8) In this method different skeletal parts are positioned by Tv fluoroscopy and automatically scanned by a beam from an X ray tube The beam com prises two wavelengths by means of which it is possible to compensate for the attenuation in the soft tissues sur rounding the bone The mineral content was determined in the forearm (radius + ulna 1 and 8 cm respectively proxi

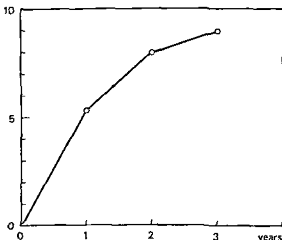


Fig 1 Difference in percentage change in bone mineral content between postmenopausal women treated with female sex hormones and controls The plot represents the mean of 4 measuring sites

Table I *Bone mineral content in controls and in women treated with sex hormones at the start of the treatment*

	Controls (mg/mm)		Hormone treated (mg/mm)		Difference		
	Mean	S D	Mean	S D	%	*t*	*P*
Radius + ulna distal	101	22	102	24	+1	0 10	>0 05
Radius + ulna shaft	161	25	159	31	−1	0 17	>0 05
Femur neck	259	33	245	49	−5	0 79	>0 05
Femur shaft	474	57	438	60	−8	1 44	>0 05

mal to the radiocarpal joint) and the femur (neck and shaft) The sites of measurements and their precision have been described in detail by Dalén and Jacobson (5) Measurements were made at yearly intervals over a 3 year period

The statistical evaluations were made according to Student s *t* test

RESULTS

At the start of the study there was no significant (P>0 05) difference in mineral content between women treated with sex hormone and controls (Table I) In the prospective part of the study the women treated with hormones increased their mineral content significantly (P<0 05) by 3 3% on an average per year as compared with the controls There was no correlation between change of mineral content and age in either group The greatest difference in change of mineral content between the two groups occurred at the beginning of the treatment (Fig 1)

DISCUSSION

Albright et al (2) proposed that deficiency of female sex hormones leads to osteoporosis by decreased bone formation It has however later been shown by analysis of the calcium metabolism (10) and by studies of microradiograms (12) that treatment with female sex hormones reduces the bone resorption The current view is that estrogen inhibits the resorptive effect of parathyroid hormones (9)

By the development of new radiological methods e g measurements of the bone mineral content it has been possible to quantify skeletal changes Aitkens et al (1) have convincingly demonstrated that treatment with estrogen prevents the bone mineral losses after oophorectomy and even increases the bone mineral content when treatment is given within 3 years of oophorectomy The bone mineral losses after oophorectomy are particularly high in trabecular bone that is in parts of the skeleton where older women show a high incidence of fractures (3 6)

From a clinical point of view it is of particular interest to know whether treatment with female sex hormones can prevent the bone mineral losses normally occurring in women from their fourth decade These physiological bone losses possibly have multifactoral etiology For instance older women often have a low calcium intake due to lactase deficiency (4) Therefore the conditions after artificial and natural menopause are not quite comparable

In the present study the bone mineral con

Table II *Annual change in mineral content in controls and in women treated with sex hormones*
The change has been expressed as a percentage of the initial values in the respective groups

	Controls (%)		Hormone treated (%)		Difference		
	Mean	S D	Mean	S D	%	*t*	*P*
Radius + ulna distal	+1 7	7 6	+7 1	4 6	+5 4	2 03	>0 05
Radius + ulna shaft	−0 5	3 2	+2 0	4 6	+ [illegible] 5	1 50	>0 05
Femur neck	+1 2	4 7	+4 7	5 1	+3 5	1 66	>0 05
Femur shaft	−2 9	2 5	−0 9	2 6	+1 9	1 75	>0 05
Mean of four sites	−0 1	3 9	+3 2	3 3	+3 3	2 16	<0 05

...ned in those women treated with sex ...ones A similar result has been reported by ...ema et al (11) who found in 6 women with ...menopause an increase of the bone mineral ...ent during treatment with various estrogens ... a 6-year period In accordance with their ...es the change in bone mineral content did not ...e with the age of the patients Thus ...one treatment seems to have an effect on the ...eleton even if the patient passed the menopause ...eral years previously

Riggs et al (12) have suggested that the effect of ...ment with female sex hormones decreases with ...e as judged from findings on microradiograms ...n long-term treatment the bone formation is ...ressed after an initial inhibition of bone resorp... The shape of the curve in Fig 1 is in agree... with the concept that the greatest effect is ...eved at the beginning of the treatment

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Submitted for publication May 5 1977

Bertil Lamke
Department of Medical Engineering
Karolinska institutet
S-104 01 Stockholm
Sweden

Acta Obstet Gynecol Scand 57 439–452 1978

ULTRASTRUCTURAL FEATURES IN NORMAL AND HYPERPLASTIC POSTMENOPAUSAL ENDOMETRIUM

Liane Deligdisch G Yedwab A Persitz and M P David

From the Governmental Municipal Hospital of Tel Aviv (Ichilov) Tel Aviv Medical School Israel

Abstract Seven samples of po tmenopausal endometrium were studied by electron microscopy Four samples were diagnosed as adenomatous hyperplasia (? of which were atypical) and 3 as normal postmenopausal endometrium The most striking ultrastructural features of hyperplastic endometrium were numerous nucleoli deep nuclear membrane infoldings increased nucleocytoplasmic ratio prominent and enlarged RER closely associated with mitochondria and nuclear membrane abundant free ribosomes and marked network microfilaments In the case of atypical adenomatous hyperplasia the protruded intraglandular *proliferating epithelial* cells exhibited more atypical features than the epithelial cells of the glandular lining suggesting a more advanced degree of the plastic change The characteristic features of the normal postmenopausal endometrium were paucity and random distribution *of the cytoplasmic organelles the presence* of large cytoplasmic vacuoles and short blunt microvilli Secretory vacuoles opening into the lumen of the gland were found in one case of cystic atrophy of a normal postmenopausal endometrium Collagenization was found in the *stroma of both groups although predom*inantly in the normal postmenopausal endometrium In ? cases of adenomatous hyperplasia stromal cells with vacuolar cytoplasm were found The significance of these findings as related to their importance as precursor stages of endometrial cancer *(in the cases of adenomatous and* atypical adenomatous hyperplasia) as involutional manifestations (in the cases of normal *postmenopausal en*dometrium) and as related to the absence of cyclic activity (in both groups) is *briefly discus ed*

The precursor stages of endometrial carcinoma are now well documented *(5)* According to the classification of Vellios (10) adenomatous hyperplasia atypical hyperplasia *and carcinoma in situ* represent the steps in the natural history of endometrial carcinogenesis

The incidence of the precursor stages of endometrial carcinoma is *high in postmenopausal* women and few reports on the ultrastructure of the normal postmenopausal endometrium *are published* thus far. A comparative study of the ultrastructural characteristics of normal and hyperplastic postmenopausal endometrium was undertaken

MATERIALS AND METHODS

Samples of endometrium from 7 patients selected according to age group (47 to 52) and postmenopausal interval (2 to 4 years after onset) were studied by light and electron microscopy The histopathological diagnoses were adenomatous hyperplasia in ? cases atypical adenomatous hyperplasia in ? cases inactive postmenopausal endometrium in 2 cases and inactive postmenopausal endometrium with cystic atrophy in one case

The material was obtained by endometrial curettage followed by hysterectomy in the two cases of atypical hyperplasia of the endometrium The histopathologic diagnosis was based on both endometrial curettings and *samples obtained from the hysterectomy specimen*

The tissue was fixed in buffered glutaraldehyde for hours dehydrated in ethanol and embedded in Epon 81? Thick sections were first cut with the Porter Blum MT ultramicrotome and stained with toluidine blue in order to *localize the areas cho en for ultrathin sections which were* then stained with lead citrate and uranyl acetate Observation sections and photography were carried out on JEM The sections for light microscopy were fixed in formalin sections of 4 μm prepared in the usual way and stained *with hematoxylin and eosin*

RESULTS

Light microscopy revealed the presence of crowded glands intraglandular bridging and pluristratification *of the tall columnar epithelium in the en*dometrial glands of all 4 cases diagnosed as *adenomatous and atypical adenomatous hyper*plasia Cellular atypia was more marked in the 2 *cases of atypical adenomatous hyperplasia in* which numerous mitotic figures nuclei with an ir*regular chromatin pattern and prominent nucleoli* were found Glands in glands papillary projec*tions and clusters of epithelial cells in the glandular* lumen were frequently observed

The normal postmenopausal endometrium was thin and the glands mostly small and lined by a single layer of cuboidal epithelium Several dilated and cystic glands with an amorphous eosinophilic

Table I *Nuclear ultrastructural changes in Endometria*

	Nucleo-cytopl ratio	Nuclear infolding	Size of nucleoli	No of nucleoli	Perinuclear location of RER	Nuclear shape
10? AH	Moderately *increased*	Deep	Increased	3–4	Frequently *present*	Irregular or ovoid
103 PM	Decreased	Shallow	Normal or decreased	1–3	Absent	Round
104 PM	Decreased	No infoldings	Small to normal	1–2	Absent	Round
106 PM	Decreased	Shallow	Normal	1–2	Absent	Round–oval
107 AH	Increased	Deep	Increased	2–5	Present	Irregular or ovoid
109 AAH	Very increased	Deep	Increased	3–6	Present	Irregular
110 AAH	Increased	Very deep	Increased	4–5	Present	Irregular or ovoid

Table II *Cytoplasmic ultrastructural changes in endometrium*

AAH = atypical adenomatous hyperplasia AH = adenomatous hyperplasia PM = normal postmenopausal

	RER	Free ribosomes	Mitochondria	Lysosomes	Micro-filaments	Lateral membrane	Fat vacuoles
10? AH (48)	Very prominent dilated convoluted Related to nuclei and mitochondria	Very abundant	Numerous crowded Mainly sub nuclear	Numerous diffuse	Well developed	Slightly infolded	Absent
103 PM (5_)	Poorly developed Unrelated to mitochondria	Relatively poor	Few random location	Rare	Almost absent	Indented or straight	Large light numerous pushing organelles
104 PM (50) cystic	Moderately devel oped Unrelated to mitochondria	Numerous	Numerous random location	Numerous apical area	Moderately developed	Indented	Numerous da and light secr into lumen
106 PM (48)	Well developed Unrelated to mitochondria	Poor	Moderately to numerous random location	Numerous mainly at apical border	Absent	Indented	Numerous secretion into lumen
107 AH (51)	Very prominent dilated related to mitochondria	Very numerous	Numerous random location	Poor	Well developed	Straight	Absent
109 AAH (47)	Very prominent & dilated related to mitochondria & nuclei	Very numerous	Numerous increased in size	Moderate	Well developed	Straight	Absent
110 AAH (49)	Very prominent & dilated In stacks para llel Related to nuclei and mitochondria	Generally abundant Reduced in some cells	Numerous sub and supra nuclear	Numerous	Well developed	Straight	Absent

Age of patient in parantheses

content were found in one case The stroma was dense

The ultrastructural changes of the nucleus and various cytoplasmic organelles are summarized in Tables I and II The comparison between the major findings in the normal postmenopausal and the hyperplastic postmenopausal endometrium is summarized in Table III

An obvious characteristic of the epithelial cells in the hyperplastic endometrium absent in the normal postmenopausal endometrium was the finding of prominent and convoluted Rough Endoplasmic Reticulum (RER) with a definite close relationship to mitochondria and nuclei (Fig 1) Also found in the samples of hyperplastic endometrium was a delicate network of microfilaments found mainly perinuclear or between the mitochondria (Fig 2) The nuclear characteristics found in all cases of hyperplasia were deep indentations of the nuclear membrane an increased number of nucleoli (2 to 6) and clumps of chromatin throughout the nucleus (Fig 3)

The dominant characteristic of the normal postmenopausal endometrium was the presence of numerous vacuoles in the cytoplasm of the epithelial cells These were clear greyish or dark and pushed the cytoplasmic organelles to random locations (Fig 5) Also found in the normal postmenopausal endometrium were epithelial cells with short blunt microvilli and an abundant collagen in the stroma Collagen formation however was present also in 2 cases of hyperplasia (Fig 6) Glycogen in the cytoplasm was poor or absent A special feature was the frequent finding of secretory vacuoles opening into the glandular lumen (Fig 7) in the sample in which light microscopy showed

...p	Glycogen	Stroma	Cilia	Microvilli	Protruding epithelial cells into glandular lumen
...r	Relatively poor	Numerous collagen fibers Cells with fat droplets	Present	Normal length	– –
...r	Absent	Abundant collagen fibers	Present	Short blunt	–
	Absent	Abundant collagen	Absent	Normal length	–
...vera e	Absent	Abundant collagen	Absent	Short blunt	–
...derate	Present	Moderate collagen	Present	Normal length	–
...ra.e	Present	Poor collagen abundant fat droplets	Present	Normal length	Present
	Relat poor	Moder collagen Numerous fat droplets	Absent	Normal length	Present

Table III *Comparative ultrastructural findings in normal and hyperplastic postmenopausal endometrium*

Nuclear characteristics

	Nucleo cytoplasmic ratio	Nuclear infolding	No of nucleoli	Perinuclear locations of RER	Nuclear shape
PM	Decreased (3)	Shallow (2) Absent (1)	1–2 (?) 1–3 (1)	Absent all	Round–oval all
AH & AAH	Increased (4)	Deep (4)	2–6 (4)	Present all	Irregular (3) oval (1)

Cytoplasmic characteristics

	PER	Free ribosomes	Mitochondria	Lysosomes	Microfil aments	Lateral Membranes	Fat vacuoles [illegible]
PM (3)	Poorly developed (1) Moder developed (2) Unrelated to mitochondria (3)	Numerous (1) Poor (?)	Numerous (1) Few (2) Random location (3)	Numerous (2) Rare (1)	Absent (?) Moderately developed (1)	Infolded (3)	Present (3)
AH ( ) AAH	Increased Dilated Related to mitochondria (4)	Very numerous (3) Reduced (1)	Numerous (4) Mainly subnucl (3) Supranucl (1)	Numerous (?) Moderate (1) Rare (1)	Well developed (4)	Infolded (1) Straightened (3)	Absent (4)

cystic atrophy of the endometrium The nuclei were mostly round and contained 1–3 nucleoli

A peculiar finding in the cases of atypical adenomatous hyperplasia was the protrusion into the glandular lumen of epithelial cells exhibiting an exaggeration of the characteristics found in the epithelial lining of the endometrial glands such as increased nucleo-cytoplasmic ratio depth of nuclear infoldings abundance of free ribosomes and RER Also seen in these cells were straightened lateral cell membranes (Fig 4)

DISCUSSION

Numerous detailed descriptions of the ultra structure of the normal endometrial cycle (1 2 8 11) of endometrial carcinoma (4 9) and recently of endometrial hyperplasia (6) have been published Descriptions of normal postmenopausal endometrium are few however (7)

In our material the most prominent features of hyperplastic endometrial cells were related to in creased metabolic activity increased protein synthesis and cellular replication enlarged nuclei with deeply indented nuclear membrane abundant convoluted and dilated RER with a peculiar close association to mitochondria and nuclear membrane These features were absent in all cases of normal postmenopausal endometrium in which mito chondria were less abundant and randomly located free ribosomes poorly represented and microfila ments poorly developed or absent The nuclei in the normal postmenopausal endometrial cells were round with fewer nucleoli suggesting together with their cytoplasmic characteristics a paucity of the organelles concerned with anabolic cell functions

Degenerative changes also appear to take place in the cytoplasm of the epithelial cells of the post menopausal endometrium The finding of large vacuoles probably fatty in nature although the Sudan staining of the light microscopy sections was negative occupying a large part of the cytoplasm and pushing the organelles (Golgi mitochondria

...p	Glycogen	Stroma	Cilia	Microvilli
s( ) erate	Absent (3)	Abundant collagen (3) Lipids in cells absent (3)	Present (1) Absent (?)	Short blunt (?) Normal (1)
r(?) dr ( )	Present (?) Rel poor (?)	Abundant collagen (?) Poor collagen (?) Lipids in cells present (4)	Present (3) Absent (1)	Normal length (4)

etc) to random locations could suggest the beginning of a cellular breakdown

The finding of vacuolar structures opening into the glandular lumen in the case of cystic atrophy in a normal postmenopausal endometrium may illustrate the mechanism of formation of the cystic structures by an accumulation of amorphous material originating from cellular breakdown

In both cases of atypical adenomatous hyperplasia areas of proliferating endometrial epithelial cells protruding into the glandular lumen were studied at the ultrastructural level Two findings seem to be of interest

1) A straightening of the lateral cellular membranes suggesting a morphological expression of the loss of contact inhibition by loosening of the intercellular connections which is characteristic of neoplastic growth

2) An obvious exaggeration of the particular traits of the hyperplastic process in these cells suggesting that the protruded cells compared to those of the glandular lining are more anaplastic and represent a more advanced stage in the histogenesis of the endometrial cancer from its precursor stages

In one of the cases of atypical adenomatous hyperplasia in which such intraglandular protruding cells were found a hysterectomy was performed and an area of endometrial adenocarcinoma was found on random light microscopy examination (case 109)

The network of delicate microfilaments described as interconnecting the RER free ribosomes and perinuclear space is probably involved in cellular anabolic activity and active proliferation It was absent in 2 of the 3 normal postmenopausal endometria and present in all of the 4 cases of adenomatous hyperplasia These microfilaments were also found in endometrial carcinoma and described as unrelated to the degree of differentiation of the tumor (9)

Other ultrastructural features such as the presence of various lysosomes the absence or poor representation of the Golgi apparatus and of the glycogen granules were found in both normal and hyperplastic postmenopausal endometrium and seems to be consistent with the lack of cyclic activity in both groups

The presence of ciliated epithelial cells in some endometrial glands of both groups could be related to certain estrogenic influences (9) although no marked differences were found

The stromal cells contained fat droplets in 2 of the hyperplastic postmenopausal endometrial samples which is consistent with the occasional finding of foamy histiocytes in the stroma of the atypical hyperplastic endometrium at light microscopy This finding was considered as a reflection of hyperestrogenism

There were no such stromal cells in the normal postmenopausal endometrium Collagen formation in the stroma was marked in the normal postmenopausal endometrium and present in 2 hyperplastic postmenopausal samples and seems to be related to the absence of cyclic activity

Although performed on a relatively small number of samples this study brought us an insight into some of the ultrastructural characteristics of a preneoplastic state (the adenomatous and atypical adenomatous hyperplasia) of the mechanism of involution of an inactive tissue (the normal postmenopausal endometrium) and of ultrastructural features related to the absence of cyclic activity of the endometrium

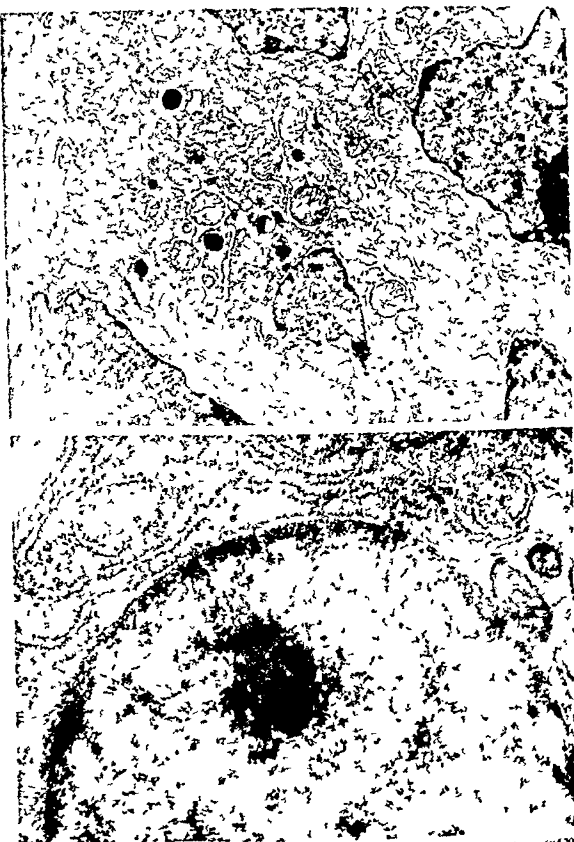


Fig. 1. Top: Adenomatous hyperplasia. Prominent RER (rough endoplasmic reticulum) surrounding closely the mitochondria and the nuclear membrane (×5 ?00). Bottom: Same at higher magnification (×? 800).



† 2 Adenomatous hyperplasia Microfilaments located
tween the nucleus and mitochondria (×17 000)

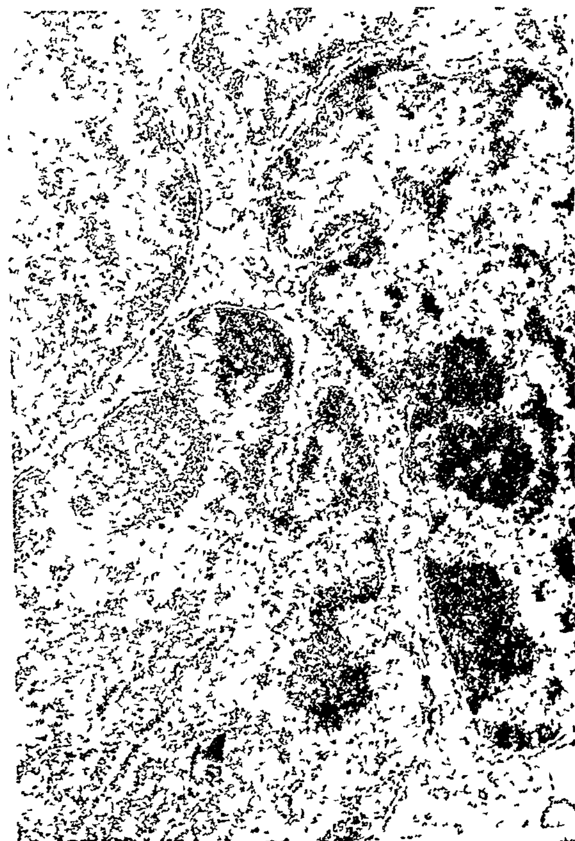
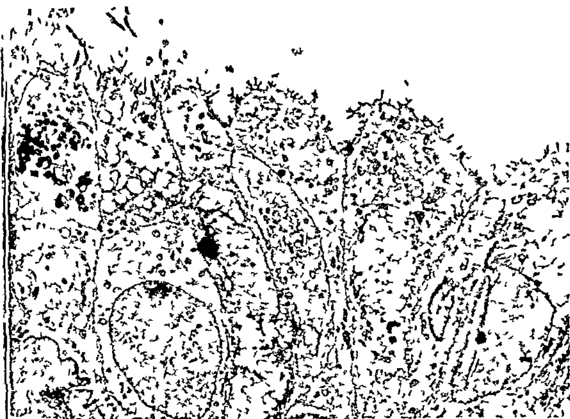


Fig 3 Atypical adenomatous hyperplasia Increased nucleocytoplasmic ratio deep infoldings of nu lear infoldings of nuclear membrane irregular and coarse chroma a pattern (×15 500)



Fig 4 Atypical adenomatous hyperplasia Group of epithelial cells protruding into the endometrial lumen Note the exaggeration of anaplastic features in this group of cells compared to the glandular lining such as increased nucleo-cytoplasmic ratio numerous nucleoli coarse and irregular chromatin (×3400) *Upper figure* an individual cell starting to protrude into the endometrial lumen Arrow shows the straightened lateral cell membrane (×7900)





ig 5B Normal postmenopausal endometrium The ytoplasmic vacuoles are partly dark and partly clear and ush the cytoplasmic organelles to random locations Note occasional ciliated cells The microvilli are short and blunt (×1_600)

Fg 5A Normal postmenopausal endometrium The epithelial cells are cuboidal the nuclei rounded with few ..leoli The cytoplasm contains numerous clear vac oles In the stroma collagen is abundant surrounding stroma cells (×15 300)

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Submitted for publication April 1 1977

Liane Deligdisch
The Mount Sinai Hospital
Fifth Avenue and 100th Street
New York
NY 10029
USA

Acta Obstet Gynecol Scand 57 453–455 1978

VULVOVAGINAL CANDIDIASIS IN PREGNANCY TREATED WITH CLOTRIMAZOLE

Kjell Haram and Asbjorn Digranes

From the Department of Obstetrics and Gynecology and the Gade Institute Department of Microbiology University of Bergen Bergen Norway

Abstract An open trial of local clotrimazole therapy in 56 pregnant women with vulvovaginal candidiasis is reported The diagnosis was confirmed by mycotic culture The patients were given one vaginal tablet daily and cream was applied to the vulva 2 or 3 times daily Their male partners were treated with cream only The duration of therapy was 6 days Fifty of the patients (89 3%) were clinically cured after 6 days of therapy Six patients (10 %) had slight complaints and 10 (17 9%) without symptoms or signs of infection harboured *Candida albicans* or other yeast species in the genital tract Six of the patients were given a second treatment with clotrimazole and their remaining symptoms subsided Candidiasis recurred later in pregnancy in 4 of the 56 patients studied The implications of the presence of Candida in the genital tract are discussed It is concluded that clotrimazole is an effective antimycotic agent which can be used for vulvovaginal candidiasis during pregnancy without causing side effects Two of the patients had trichomoniasis concurrently One one of these was cured with clotrimazole

An association has been reported between pregnancy and impaired immunological function (6 8 10 13 15) Cellular immunity in the host is fundamental for the defence against viral and fungal diseases Vulvovaginal candidiasis is common during pregnancy and it is conceivable that cellular immunity is involved In addition it is thought that an action of oestrogen from the placenta on carbohydrate metabolism promotes the growth of yeast in the lower genital tract (1 2)

The presence of Candida does not indicate manifest candidiasis (11) However inflammatory changes and particularly obvious vulvitis represent definite fungal disease

As pregnancy predisposes to candidiasis and treatment is indicated it is valuable to test the effect of antimycotic agents in pregnant women

The purpose of the present study was to investigate the effect of clotrimazole on manifest vulvovaginal candidiasis in pregnancy using the recommended medication

MATERIAL AND METHODS

Fifty six pregnant women were investigated Age length of gestation and duration of symptoms at the start of therapy are shown in Table I Seven patients had had some other form of antimycotic treatment earlier during the pregnancy None of the patients were diabetics All had vaginal discharge itching and burning pain in the vulva and obvious vulvar inflammation High vaginal swabs were inserted into Stuart s transport medium and brought to the microbiological laboratory The specimens were cultured on Sabouraud dextrose agar The plates were incubated at 25 C for 4 days Isolates of *Candida albicans* were identified by the production of germ tubes in human serum (5) Other yeast species were not identified All specimens were also examined for *Trichomonas vaginalis* using Diamond s substrate (3) as the culture medium After inoculation the tubes were incubated at 37°C Microscopical examination of material from the tubes was performed after 2 days and when found negative after a further 3 days

The patients were treated with one clotrimazole (100 mg) vaginal tablet daily for 6 days and in addition cream was applied to the vulvar area 2 or 3 times daily Their male partners were not examined but were treated with clotrimazole cream The patients were advised not to have sexual intercourse during this period

The women were examined 3 weeks after the commencement of treatment Patients with persistent vulvitis were given an additional period of treatment with clotrimazole Those without symptoms were checked with a second mycotic culture

The patients were followed until parturition but no further mycotic culture was done and the patients were not examined in the puerperium Recurring vulvovaginal candidiasis was however treated with the same agent

Table I *Clotrimazole therapy in 56 pregnant women with vulvovaginal candidiasis Age length of gestation and duration of complaints*

	Mean (range)
Age (years)	27 1 (17–36)
Gestation length (weeks)	4 7 (8–33)
Duration of complaints (weeks)	11 4 (1–33)

Table I *Bladder pressure (BP) maximum urethral pressure (MUP) closure pressure (CP) and functional length of the urethra (FUL) in 16 healthy females at a bladder volume of 200 ml*

Patient	BP (cmH_2O)	MUP (cmH_2O)	CP (cmH_2O)	FUL (mm)
1	6	46	40	24
2	20	96	76	38
3	20	108	88	30
4	20	95	75	30
5	28	136	108	30
6	16	75	59	25
7	24	96	72	28
8	24	115	91	32
9	18	97	79	32
10	20	106	86	41
11	20	57	37	37
12	10	101	91	28
13	20	60	40	34
14	20	91	71	33
15	8	77	49	26
16	28	77	49	26
Mean	20	90	69	31
R	6–28	46–136	37–108	24–24

transducer of the recording catheter was placed at that site in the urethra of maximal intra urethral pressure (Fig 1) The infusion of saline was then continued at the same rate as before

During the simultaneous recording of the intravesical and intraurethral pressures at increasing bladder volumes the women were requested to announce when they had sensations of urgency and wanted to void At that time the infusion catheter was withdrawn and the women were allowed to micturate

The recordings were performed with the subjects in the sitting position

For the first five examinations the abdominal pressure was recorded by means of an intrarectal micro-transducer Simultaneous bladder and urethral pressures were registered to obtain a true detrusor pressure Since the intrarectal pressure recording apparently did not give additional information it was not used in subsequent investigations

After the investigations were completed the residual urine was measured and a sample sent for bacterial culture These tests were repeated on the 10th day after the investigations

Before and after the examination the recording equipment including the catheter was calibrated as described previously (Asmussen Lindstrom & Ulmsten 1975)

Recorded parameters

The following parameters were measured (see Tables I–IV and Figs 1–4) bladder pressure maximum urethral pressure urethral closure pressure i e the difference between maximum urethral pressure and the bladder pressure bladder volume at voiding detrusor latency time i e the time interval between the decrease in urethral pressure and detrusor contraction (Fig 2) "pre voiding time" i e the time interval between the decrease in urethral pressure and zero closure pressure (Fig 2) the residual urine after voiding

RESULTS

The findings in the healthy females are given in Tables I and II and in Fig 2 As can be seen when

Table II *Bladder pressure (BP) maximum intra urethral pressure (MUP) and closure pressure (CP) just before initiation of voiding bladder volume (BV) at voiding detrusor latency time (dlt) pre voiding time (pvt) and residual urine (RES) after voiding in 16 healthy females*

Patient	BP (cmH_2O)	MUP (cmH_2O)	CP (cmH_2O)	BV (ml)	dlt (sec)	pvt (sec)	RES (ml)
1	0	76	56	400	0 8	4 8	0
2	24	128	104	500	5 0	10	0
3	24	104	80	475	1 4	2 0	[illegible]
4	32	104	72	450	4 6	6 0	2
5	28	136	108	375	1 [illegible]	4 8	6
6	20	79	59	375	2 0	4 0	2
7	8	96	68	250	2 5	[illegible] 5	2
8	32	148	116	350	5 0	12	1
9	36	140	104	500	[illegible] 5	7 0	0
10	4	114	90	350	4 0	6 0	1
11	4	69	45	350	4 0	8 0	[illegible]
12	0	112	92	400	2 5	3 0	6
13	24	72	48	400	1 6	11	6
14	24	91	67	500	6 4	8 4	3
15	40	97	57	300	2 0	4 0	5
16	60	117	57	450	[illegible] 4	3 6	4
Mean	9	105	76	40[illegible]	3 0	6 [illegible]	[illegible]
Range	0–60	69–148	45–116	250–500	0 8–6 4	[illegible] 0–12	0–6

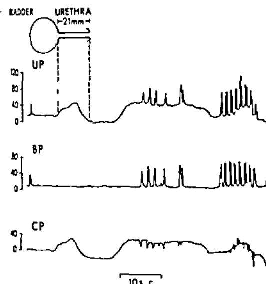


Fig 1 Simultaneous recordings of urethral pressure (*UP*) bladder pressure (*BP*) and closure pressure (*CP*) i.e. the difference between urethral pressure and bladder pressure Left part of the tracings recording of the urethral closure pressure profile Right part of the tracings recording of pressure changes during repeated coughing

the bladder filling increased from 200 ml to the volume at which voiding occurred there was a mean increase in bladder pressure from 20 cm H_2O to 29 cmH_2O and in maximum intra urethral pressure from 90 cmH_2O to 105 cmH_2O Immediately before voiding the maximum intra urethral pressure decreased A few seconds later (mean 3 0 sec see dlt in Table II) the intravesical pressure increased As a result of these pressure changes the urethral closure pressure decreased to zero This occurred after a mean of 6 2 sec (see pvt in Table II) and at this time urine started to escape the urethra (Fig 2) The bladder volume at which the women wanted to micturate varied between 250 ml and 500 ml (mean 400 ml) and they were all able to empty their bladders completely (Table II)

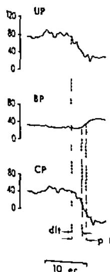


Fig 2 Recordings of urethral pressure (*UP*) bladder pressure (*BP*) and closure pressure (*CP*) in a healthy woman at the initiation of voiding *dlt*=detrusor latency time *pvt*=pre voiding time

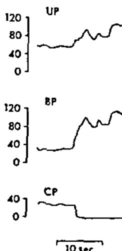


Fig 3 Recordings of urethral pressure (*UP*) bladder pressure (*BP*) and closure pressure (*CP*) in a woman initiating voiding by the Valsalva manoeuvre

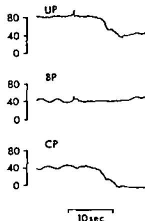


Fig 4 Recordings of urethral pressure (*UP*) bladder pressure (*BP*) and closure pressure (*CP*) in a woman initiating voiding mainly by decreasing the urethral pressure

Table III *Bladder pressure (BP) maximum urethral pressure (MUP) closure pressure (CP) and functional length of the urethra (FUL) in 13 patients with stress incontinence at a bladder volume of 200 ml*

Patient	BP (cmH O)	MUP (cmH_2O)	CP (cmH_2O)	FUL (mm)
1	27	63	36	22
	16	44	28	32
3	.8	88	55	33
4	6	66	60	34
	8	48	40	30
6	20	44	24	16
	24	61	37	44
8	3	72	40	29
9	28	84	56	30
1	32	92	60	.8
	24	50	26	20
1	1	60	48	33
13	12	44	32	31
Mean	21	63	42	29
Range	6–32	44–92	24–60	16–44

The results obtained in the stress incontinent patients are shown in Tables III and IV and in Figs 3 and 4 The mean maximum urethral pressure and the mean closure pressure at a bladder volume of ml were lower in these patients than in the healthy women However the mean bladder pressure was the same 20 cmH_2O When the bladder volume increased from 200 ml to the volume at which voiding occurred the intravesical pressure increased to 29 cmH_2O In contrast to what was found in the normal women there was simultaneous increase in maximum urethral pressure In 5 of the patients (Nos 1–5 in Table) micturition was initiated by the Valsalva manoeuvre (Fig 3) Three patients (Nos 6–8 in Table IV) initiated voiding mainly by decreasing the maximum urethral pressure (Fig 4) The remaining patients (Nos 9–13 in Table IV) initiated voiding mainly in the same way as the healthy females The bladder volume at which the patients wanted to void varied between 300 ml and 800 ml (mean ml) and some of them had difficulty in emptying their bladders completely (Table IV)

DISCUSSION

It must be emphasized that voiding in a laboratory implies an unpleasant situation for a female G efforts should therefore be made to allow the patient to adapt to the recording situation and measuring equipment used should be as easily handled as possible in order not to influence the responses The recording technique used in this st allowed 29 out of 32 patients to void promptly as they said in their normal way during the investigations

Most studies of micturition in the female h

Table IV *Bladder pressure (BP) maximum intra urethral pressure (MUP) and closure pressure (CP) before initiation of voiding bladder volume (BV) at voiding detrusor latency time (dlt) pre voiding (pvt) and residual urine (RES) after voiding in 13 women with stress incontinence*

Patient	BP (cmH_2O)	MUP (cmH O)	CP (cmH_2O)	BV (ml)	dlt (sec)	pvt (sec)	RES (ml)
1	35	63	8	400	–	0 8	45
2	36	44	8	500	–	0 8	30
3	36	88	52	700	–	12	50
4	18	66	48	500	–	0 2	1.5
5	10	48	38	300	–	0 8	80
6	24	44	.0	325	2 0	2 0	3
7	28	49	21	300	0 8	0 8	[illegible]
8	36	84	48	325	4 0	3 [illegible]	4
9	3	72	40	300	9 6	14	10
10	5	80	28	400	1 0	1 6	8
11	28	58	30	300	0 8	4 8	1
12	28	40	12	800	1 0	3 0	60
13	20	44	.4	350	1 2	4 4	20
Mean	29	60	31	4.3	2 6	3 7	35
Range	10–52	40–88	8–5.	300–800	0 8–9 6	0 2–14	

een carried out as pressure flow studies which means recording the intravesical pressure and the flow of urine through the urethra (see Hjälmås 1976) Doubtless such a recording technique gives valuable information about micturition in the male though it seems to be of minor value in the female in whom outflow obstructions are less frequent Furthermore it does not permit detailed studies of the interplay between the urethra and the bladder at the very initiation of micturition In the few studies of micturition in females performed with simultaneous intra urethral and intravesical pressure recordings relatively wide bore catheters have been used (Karlsson 1953 Enhorning 1961) A urethral catheter always implies a risk of disturbing normal micturition in particular there is a risk of obstructing the flow of urine through the urethra as it has been shown that the urethral lumen during micturition seldom exceeds 3–4 mm (Smith 1968) As the recording catheter used in this study has an outer diameter of 1 6–2 2 mm it should reasonably give minimal obstruction to the flow of urine

Technically the present recording equipment has important advantages compared with previously used techniques for study of the initiation of micturition in females It is easy to calibrate and to handle It measures the intravesical and the intra urethral pressure as well as the urethral closure pressure related to atmospheric pressure and no fluid is necessary for the recordings

Compared with balloon catheters and open end catheters the micro-transducer catheter has a better frequency response The micro-transducer can adequately record pressure changes occurring faster than 10 msec (Asmussen Lindstrom & Ulmsten 1975) which is more than sufficient for the changes occurring in the lower urinary tract

The present investigation confirms a preliminary report concerning initiation of voiding in healthy females (Ulmsten Andersson & Persson 1975) Thus in the healthy females micturition commenced by an initial decrease in the urethral pressure followed by increase in the intravesical pressure Generally speaking the urethral closure pressure reached zero within 6–7 seconds after the females were allowed to void

The cause of the observed pressure changes cannot be determined by the present investigation but there is reason to believe that the rapid initial decrease in urethral pressure was mainly caused by a voluntary relaxation of the striated muscles in the pelvic floor partly supplying the urethra (Öbrink Ingelman Sundberg & Ulmsten 1977a) whereas the increase in bladder pressure indicated activation of the detrusor

Influences from the autonomous nervous system might also contribute to the actual pressure changes Thus in cats an increased activity in the sympathetic nervous system has been shown during the filling phase of the bladder (Edvardsen 1968) Stimulation of beta adrenoceptors predominating in the bladder wall diminishes the increase in bladder pressure obtained when increasing bladder volume (Edvardsen 1968) Conversely stimulation of the alpha adrenoceptors which predominate in the urethra (Ek Alm Andersson & Persson 1977) increases the maximal intra urethral pressure (Ek Andersson & Ulmsten 1977) The intra urethral pressure in healthy females also increased with increasing bladder volumes which finding tallies with previous findings (Ulmsten et al 1975 Öbrink Ingelman Sundberg & Ulmsten 1977b)

Thus an interruption of the sympathetic nerve stimulation to the urethra and bladder at initiation of micturition may contribute to a decrease in the intra urethral pressure and facilitate an increase in the intravesical pressure In the present investigation eight stress incontinent patients initiated micturition by decreasing the urethral pressure only or by a Valsalva manoeuvre The reasons for these modes of initiating voiding are unclear

Despite the small number of women investigated in this study the results make it of interest to discuss the consequences of surgical treatment of stress incontinent patients Thus in patients who initiate voiding by decreasing the urethral pressure only operative procedures with non absorbable slings should be carried out with caution since relaxation of the urethra might be impaired with a consequent increased risk of postoperative incomplete voiding Similarly overcorrection with traditional urethropexies using unabsorbable sutures may increase the risk of postoperative retention of urine In patients voiding by means of a Valsalva manoeuvre a sling could also complicate micturition since straining of the abdominal muscles to which the slings are attached may also cause a strain in the sling leading to a further elevation of the urethra at initiation of micturition However to estimate with certainty both qualitative and quantitative disturbances of voiding after different surgical procedures in women suffering from

continence analyses of micturition must be done before as well as after the actual surgical procedures

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Submitted for publication June 20 1977

Ulf Ulmsten
Department of Obstetrics and Gynecology
University Hospital of Malmo
S 214 01 Malmo
Sweden

Acta Obstet Gynecol Scand 57 463–468 1978

BLADDER BASE INSUFFICIENCY

Radiological Urodynamic and Clinical Aspects

Knud P Olesen and Steen Walter

*From the Department of Radiology and the Department of Urology
Gentofte Hospital University of Copenhagen DK 2900
Hellerup Denmark*

Abstract Among 4 0 consecutive patients referred for voiding cystourethrography 26% presented the picture of bladder base insufficiency (b b i) The examination was carried out as a colpo-cysto-urethrography A urodynamic and gynecological examination was performed in each patient The characteristic morphological features were anterior and inferior displacement of the bladder neck and a pointed bladder base The position and form of the vagina was normal Radiological signs of detrusor function were weak and opening of the bladder neck was characterized by funneling Urodynamically the patients with b b i showed low opening and low detrusor contraction pressures The flows were highly varying Very high flows were seen in a few patients but the more common pattern was slightly reduced maximum flow rates Opening of the internal urethral orifice is known to be caused by detrusor contraction Closing is passive caused by elastic properties in the tissues In b b i intravesical pressures during micturition were low and radiological signs of detrusor contraction were weak indicating that the bladder neck was easily opened This on the other hand means that the bladder neck was insufficiently closed during bladder reservoir function and may explain the main symptom stress incontinence which was present in 84% of the patients The underlying pathology in anatomical support and suspension of the bladder base is discussed

In the literature on female stress urinary incontinence certain clearly described morphological changes of urethra and bladder pervade Muellner (16) Ball et al (3) Roberts (21) and Ala Ketola (1) among many others have described low position and funneling of the bladder base Increase of the posterior urethro-vesical angle was reported by Jeffcoate & Roberts (13) Green (7) and Palm (20) discussed alterations in urethral inclination Hutch (12) stated that the base of the continent bladder is flat Many authors have confirmed these observations although a few have challenged one or another of the findings A few authors have doubted the value of these criteria when applied to their own examinations Hoffmann & Ulrich (11) Zacharin (24)

METHODS AND MATERIALS

Colpo cysto-urethrography (a voiding cysto-urethrogram with additional contrast medium in the vagina (Olesen & Walter (19)) was performed on 420 patients from the urological laboratory including all patients referred to the department of gynecology for utero-vaginal prolapse conditions with or without urinary symptoms A urodynamic and gynecological examination including a careful interview was performed on a separate occasion and not disclosed until a radiological diagnosis had been reached

FINDINGS

The alteration in bladder base morphology that was termed bladder base insufficiency (b b i) in a previous report by Olesen (17) was found in 110 patients (26 2%) The base is pointed with the internal urethral orifice situated at the lowest point of the bladder and lower and more anterior than normally This was diagnosed if the orifice was below the lower margin of the symphysis and the distance from the symphysis to the orifice less than 20 mm The outline of the vagina was normal with an unaltered axis and no bulgings (Fig 1*b*) The description refers to the picture of the resting bladder filled to the patient s normal desire to void This view is all that is needed for the diagnosis

In some cases the picture during cough revealed incontinence in other cases only an increase in the pointedness of the bladder base Even though a patient may suffer from stress incontinence this is not necessarily shown radiologically nor registered by the flowmeter because the cough is not spontaneous The patient is en garde We have seen this in a patient who did not show incontinence during the premediated cough but immediately afterwards had a spontaneous cough resulting in incontinence

The radiological signs of a normal





Resting filled bladder (*a*) Normal case (*b*) Bladder base insufficiency

micturition are rounding of the bladder serration of the bladder wall above the trigone and a well defined shelf like horizontal part of the bladder base in front of the internal urethral orifice as shown in Fig 2*a* It is customary to describe the opening of the bladder neck during normal micturition as a funneling This term however is not appropriate and may lead to misunderstanding In normal cases there is no funneling of the base until the last part of the micturition

In bladder base insufficiency however opening of the bladder neck involves funneling as shown in Fig 2*b* The absence of the anterior flat part is typical Rounding of the bladder is the only constantly present sign of detrusor function Serration of the bladder wall is rare and slight The urethra is usually slender tapering evenly to the external striated sphincter Variations in calibre are seen from one micturition to another and during the progress of the same micturition The urethro-pelvic angles described by Olesen & Walter (19) are normal

The above described micturition was seen in 68 cases Among the remaining patients 22 showed a sliding of the entire bladder base down in front of the vagina an anterior or prevaginal bladder descensus The urethro-pelvic angles were subnormal that is below 70 This produced an eversion of the anterior vaginal wall into the introitus but no alteration in vaginal axis or position This anterior bladder descensus was most pronounced in ... and sometimes disappeared completely towards the termination of micturition Most often the ... ical pressure measurement showed this condition to be associated with straining Another 16 patients showed a posterior descensus position during micturition that is with a displacement of the vagina in a postero-inferior direction and a central vaginal bulge Two patients could not micturate during the examination and 2 showed signs of previous operations

URODYNAMICS

Cystometrically 4 patients displayed uninhibited detrusor contractions indicating a suprasacral neurogenic bladder paresis according to Hald (...) Their symptoms were dominated by urge incontinence The remaining patients had normal cystometrograms

To describe the urodynamic picture in pure ... we exclude all patients who demonstrated descensus during micturition in the radiological examination The 4 patients with a ... neurogenic dysfunction are also excluded Two of the remaining 64 patients did not go through a full urodynamic examination

The urodynamic values are calculated as the





2b

Fig 2 Micturition (*a*) Normal case (*b*) Bladder base insufficiency

mean values of 3 micturitions the variations in each patient are not shown

The pressure rise at the start of the micturition is described as opening pressure minus premicturition pressure The values are shown in Fig 3 The average is slightly lower than normal values published by Zinner & Paquin (25) Backman et al (1) Palm (20) and Frimodt Møller (6) The detrusor contraction pressure is defined as mean micturition pressure minus premicturition pressure The values are shown in Fig 4 Zinner & Paquin (25) and Frimodt Møller (6) give normal values which the pressure values in b b i are lower than normal Uro-flow is determined as the maximum flow rate and displayed in Fig 5 These values were within the normal range

Bladder volumes varied from 175 to 500 ml The duration of micturition (flow time) was extremely variable The lowest was 12 sec at a bladder volume of 200 ml The highest was 66 sec at a volume of 450 ml

CLINICAL FINDINGS

The gynecological examination revealed some laxity or bulging of the anterior vaginal wall in 70 patients Vaginal repair operations had been performed in 25 patients One patient had had an urethropexy Hysterectomies had been performed in 15 cases Age and parity distribution (Fig 6) was an almost exact replica of the distribution of all 420 patients

Stress incontinence was a symptom in 92 patients (83 6%) Urge incontinence was the major complaint in 6 patients Two patients gave straining as their main symptom while one suffered from recurrent cystitis Nine of the patients had no urological symptoms

DISCUSSION

In the literature the pointed appearance of the bladder base is widely described as funneling The low and anterior position of the bladder neck also con

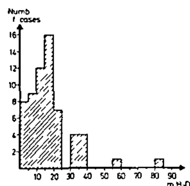
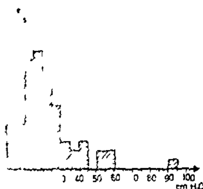


Fig 3 Bladder base insufficiency Opening pressure minus premicturition pressure $\bar{x}$ 17 0 ± S D 13 7 cmH₂O 67 cases



[illegible] Bladder base insufficiency Detrusor contraction [illegible] (mean intravesical pressure minus premicturition [illegible] 22 2±15 8 cmH$_2$O 62 cases

[illegible] with the findings of numerous previous au[illegible] (23) Hodgkinson (9 10) and Ala[illegible] give surveys of this literature We found [illegible] normal position and course of the urethra [illegible] is in accordance with Green s type I or a [illegible]sus of the bladder during micturition which [illegible]forms with Green s type II (7) We did not measure the posterior urethro-vesical angle because we have found it to vary from 100 to 180° in continent women In b b i however the downward forward sliding of the bladder base in front of the unaltered vagina necessarily tends to increase the angle which is in a cordance with the original observation made by Jeffcoate & Roberts (13)

Furthermore we agree with Béthoux et al (4) who on the basis of colpocystograms describe 2 bladder suspension defects type A that leaves the vagina unaffected and type P that produces [illegible] bulge of the anterior vaginal wall but no [illegible] in vaginal position Lazarevski et al (15) [illegible] these findings and conclude that the 2 types A and P correspond to Green s types I and II

The radiological signs suggest weak [illegible] function in b b i This is in accordance [illegible] urodynamic finding of rather a low opening pressure and detrusor contraction pressure [illegible] cates that little effort is needed for the active [illegible]ing of the bladder neck On the other hand [illegible] also account for the major symptom of these [illegible]men Stress incontinence The bladder [illegible] reduced resistance to passive opening [illegible] creases in abdominal pressure

Why is the closing of the internal urethral [illegible] insufficient? Opening of the orifice is active [illegible] by detrusor contraction Closing is passive as [illegible] distinct circular sphincter exists as shown [illegible] sections by Krantz (14) and Tanagho & Smith [illegible] Such a passive closing mechanism cannot be [illegible]pected to possess any high resistance to opening unless properly supported from the outside

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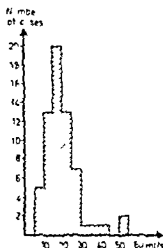


Fig 5 Bladder base insufficiency Maximum flow rates $\bar{x}$ 19 3±8 9 ml/sec 63 cases

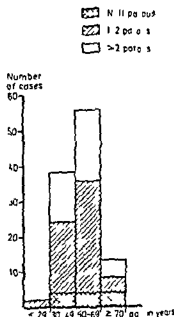


Fig 6 Bladder base insufficiency Age and parity [illegible]tion 110 cases

traction exerted on the bladder neck is dorsal in direction In the human the levator muscles have assumed a very definite function as support for the pelvic organs By forming a sling behind the vagina they supply the postero-inferior support of vagina and bladder On contraction the levator lifts the vagina and bladder in antero-cranial direction The anatomy of the levator however does not prevent the bladder base from sliding downwards forwards in front of the vagina as in b b i Prevention of this demands support in the opposite direction similar to that in quadrupeds A ligamentous sling around the anterior aspect of the bladder neck exerting a such postero-cranial traction does exist Zacharin (24) describes 2 fibro-elastic nodes intimately connected with the antero-lateral parts of the bladder neck Hutch (1?) describes fibres between these 2 nodes crossing the anterior aspect of the bladder neck as the precervical arc Olesen & Grau (18) have confirmed these findings and have shown that each node continues posteriorly in a strong fibro-elastic ligament the arcus tendineus fasciae pelvis that crosses the levator muscle and tapers in the levator fascia near the sciatic notch

Fig 1*a* shows a normal bladder It is clearly seen how the bladder neck is pulled by a sling in postero-cranial direction whereby the anterior part of the bladder swells out in front of the suspension giving the bladder base its anterior flat part If this suspension loosens the bladder neck will slide downwards forwards Secondarily the ligamentous connections from the symphysis to the bladder neck the pubo-vesical ligaments therefore no longer will be taught The latter is a common finding in stress urinary incontinence described by Krantz (14) and Zacharin (24)

Variations in urethral calibre were common and variations in uro-flow in each individual during the urodynamic examination were typical Flows were seen to vary from subnormal to high in the same patient Twelve patients constantly presented high flows and fairly low pressures Nine of these patients were under 50 years of age Palm (20) describes this pattern as decreased urethral resistance The more common pattern however was one of low or varying flows These variations in flow rate were independent of intravesical pressure changes and therefore must be due to variations in urethral muscular tone The varying but mostly incomplete relaxation of urethral muscular tone during micturition might hypothetically be explained as a consequence of an increased urethral closing pressure during reservoir function The explanation for an increased urethral closing pressure might be that when the closing of the internal urethral orifice is insufficient the remainder of the posterior urethra tries to maintain continence by increasing the muscular tone

CONCLUSION

On the basis of bladder and vaginal morphology we have described a pathologic entity named as bladder base insufficiency With the bladder filled but resting the bladder base is pointed and dislocated antero-distally in comparison to the normal bladder neck The vagina is in a normal position and a gynecological examination will not therefore reveal the abnormality

Female urinary continence depends on two factors The urethral closing pressure created by urethral muscular tone and as the second factor adequate suspension of the bladder neck In b b i the latter factor is deficient Normally the bladder is supported by two slingformed structures The levator muscles form a sling behind the vagina and thus support the vagina and bladder base postero-inferiorly The other is the arcus tendineus fasciae pelvis the periurethral fibro-elastic nodes and the precervical arc that form a sling from behind around the anterior part of the bladder neck and thus support the bladder neck antero-inferiorly In b b i this latter slingformed suspension or support is insufficient and the bladder neck slides downwards forwards

Urodynamically the characteristic traits are Low intravesical pressures and highly varying flows The low pressures indicate that little effort is needed by the detrusor to open the internal urethral orifice This on the other hand means that the closure of the orifice is insufficient and may well account for the complaint of these patients Stress incontinence

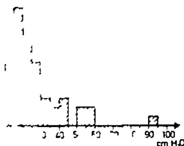
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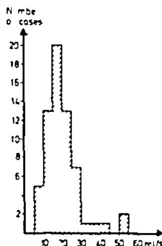


Fig 5 Bladder base insufficiency Maximum flow rates x 19 3±8 9 ml/sec 63 cases

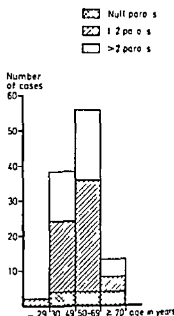


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Why is the closing of the internal urethral orifice insufficient? Opening of the orifice is a tive caused by detrusor contraction Closing is passive as no distinct circular sphincter exists as shown in the sections by Krantz (14) and Tanagho & Smith (2 Such a passive closing mechanism cannot be expected to possess any high resistance to opening unless properly supported from the outside

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Acta Obstet Gynecol Scand 57 469–470 1978

A NEW METHOD FOR PREGNANCY TERMINATION IN POLYHYDRAMNIOS

Y Beyth and N Laufer

From the Department of Obstetrics & Gynecology Hadassah University Hospital Jerusalem Israel

We wish to describe a new and safe technique for termination of anencephalic pregnancy associated with polyhydramnios which circumvents the complications of acute reduction of amniotic fluid volume in such pregnancies

CASE REPORT

A 40-year-old gravida 7 para 6 was referred to the Ultrasound Clinic in the seventh month of her pregnancy because of severe abdominal discomfort a large for date uterus with suspicion of twins Ultrasonic examination revealed a term size uterus polyhydramnios and an anencephalic fetus The diagnosis and its implications were explained to the patient Owing to emotional response as well as the serious discomfort occasioned by the abdominal distention termination of pregnancy was considered to be mandatory Due to special problems which are involved in this procedure in a grandmultipara a variation of the usual technique of instillation of hypertonic solution was employed An intraamniotic exchange transfusion with hypertonic urea solution (Urevert) was performed resulting in a high concentration of urea in the amniotic fluid (Table I) This procedure avoids acute and gross reduction of the amniotic space volume The timing of the procedure and the volumes exchanged are indicated in the table

1850 ml of amniotic fluid were removed and 600 ml of Urevert were instillated the final intraamniotic concentration of urea achieved was 5 7 g% Five hours after the end of the procedure uterine contractions started and five and a half hours later the patient delivered an anencephalic male fetus The delivery was uneventful and the patient was discharged after 3 days

DISCUSSION

Controversy exists about the management of anencephalic pregnancy with polyhydramnios diagnosed in the third trimester Those advocating a conservative policy point to placental abruption and uterine dysfunction as complications of the large reduction of amniotic fluid volume by surgical rupture of the membranes Similarly instillation of hypertonic solution to obtain high concentrations in the amniotic space require removal of a large volume of amniotic fluid in polyhydramnios with the same risk as in surgical rupture of membranes The risk of uterine rupture is particularly increased in grand multiparity and the use of prostaglandins is probably contraindicated in this situation

Table I *Exchange transfusion technique as used in the reported patient*

Timing (minutes)	Procedure	Volume (ml)	Urea concentration g
0–5	Removal of amniotic fluid	800	
6–15	Instillation of hypertonic urea	[illegible]00	
16–25	Intermission		
[illegible]6–30	Removal of amniotic fluid	800	
31–40	Instillation of hypertonic urea	[illegible]00	
41 50	Intermission		
51 55	Removal of amniotic fluid	[illegible]50	[illegible]
56–60	Instillation of hypertonic urea	[illegible]00	
61 70	Intermission		
	Removal of amniotic fluid	[illegible]	5 7

The intermissions represent periods during which fluid was neither removed nor instillated the purpose of which was to allow equilibration

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On the other hand lack of intervention is associated with serious discomfort of polyhydramnios as well as grave emotional problems Moreover an expectant policy in itself may lead to the complications mentioned above when premature rupture of membranes occurs

We have employed a modified technique of instillation of hypertonic solution which circumvents the problem of dilution by the large volume of amniotic fluid in hydramnios and prevents acute reduction of amniotic fluid volume with its attendant complications as mentioned above As described in the case report the technique of "exchange transfusion" of amniotic fluid was successful in achieving a high concentration of urea and with prompt initiation and conclusion of labor

Submitted for publication Jan 17 1978

Yoram Beyth M D
Dept of Obstetrics and Gynecology
Hadassah University Hospital
Jerusalem Israel

Acta Obstet Gynecol Scand 57 471–472 1978

SHORT COMMUNICATION

SERUM VITAMIN B_6 IN PURE PREGNANCY DEPRESSION

M O Pulkkinen J Salminen and S Virtanen

From the Departments of Obstetrics and Gynecology Sero-Bacteriology and Psychiatry University of Turku Turku Finland

High levels of steroids during pregnancy may change brain metabolism and cause depression Estrogens increase the need for pyridoxal phosphate and its deficiency is related to low brain 5-hydroxytryptamin which in turn is linked to depression (1)

Vitamin B_6 depletion may occur during pregnancy in different ways The ability of the fetal compartment to concentrate vitamin B_6 is high (3) as a result of more binding sites for pyridoxal phosphate induced by steroids Increased maternal corticosteroids induce vitamin B_6 requiring enzymes resulting in an increased binding in the mother Furthermore estrogen conjugates are known to compete with pyridoxal phosphate (5 7)

The symptoms of steroid induced depression are characterized by pessimism dissatisfaction crying and tension like in pure pregnancy depression Sleep disturbances and appetite disorders often associated with endogenous and reactive depression do not belong to this clinical picture (4) This study was designed to explore if pure pregnancy depression can be vitamin B_6-dependent

15 patients 24±0 7 years old (mean ± S E) gravida 2±0 3 para 1±0 2 were 21±6 weeks pregnant and depressed for 7±? weeks The patients were carefully selected for this study by a psychiatrist (J S) excluding other forms (endogenous reactive) of depression and patients with history of earlier clinical depression The clinical picture of pure pregnancy depression in this study was characterized by pessimism crying tension and fatigue with no sleep disturbances or appetite disorders The depth of depression was measured using the Beck Depression Inventory (BDI) ( ) Initial BDI was 17±4 (7–23 included only)

Serum B levels were analyzed microbiologically with the Saccharomyces carlsbergensis ATCC 9080 strain (6)

To check the method 7 patients were treated with ?0 mg of vitamin B_6 (Heksavit®) twice a day for one week This treatment resulted in an increase of serum concentration from 44±5 2 ng/ml to 210±32 ng/ml Low serum B reflected a deep depression ($r=0\ 56$ $p=0\ 025$ $y=-\ 6\ X+97$ Fig 1)

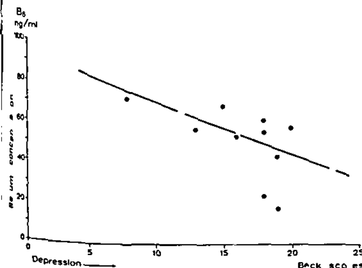


Fig 1 Correlation between the depth of pure pregnancy depression (Beck Depression Inventory) and serum B levels (microbiological method)

The present study by demonstrating a correlation between the depth of pregnancy depression and serum B_6 levels suggests that the biochemical changes (steroids → vitamin B_6) may be a cause rather than a consequence of pregnancy depression The similarity of the clinical features of pregnancy depression and depression in users of oral contraceptives (pessimism crying and tension with no sleep disturbances or appetite disorders) also supports the concept that pure pregnancy depression may be steroid induced

ACKNOWLEDGEMENTS

This work was supported by the Finnish Gynecological Research Foundation The authors are indepted to Medica Oy for drug support and for technical help to Miss Marja Aiho (vitamin assays) Mrs Arja Koivurinta (translation) Mrs Marita Vaiste (typing)

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Submitted for publication April 9 1977

Martti Pulkkinen
Dept of Obstetrics and Gynecology
University of Turku
SF 20520 Turku 52
Finland

Acta Obstet Gynecol Scand 57 473–475 1978

CASE REPORTS

THE ETHANOL GELATION TEST IN PREGNANCY

C Eika H Arnesen and H C Godal

From Hematological Research Laboratory and Department IX Ullevål University Hospital Oslo Norway

Abstract Coagulation studies in 55 healthy pregnant women indicated that in spite of high coagulation activity a positive ethanol gelation test for fibrin in plasma is not a normal feature of pregnancy The four case reports presented stress the value of the ethanol test in monitoring treatment of thromboembolic disease in pregnancy

During pregnancy increased levels of coagulation factors and reduced fibrinolytic activity are regularly observed (4 3) This hypercoagulable state is accompanied by increased risk of thromboembolic disease (11 1)

The ethanol gelation test (EGT) (7) indicates the presence of soluble fibrin in plasma and a positive test is often found during intravascular coagulation and other thromboembolic disease (9)

At Department IX Ullevål Hospital we have during recent years treated 4 pregnant patients with different manifestations of thromboembolic disease all of them having a positive EGT The positive test however might reflect the hypercoagulable state of pregnancy and as such be a normal finding in pregnancy In order to clarify the significance of a positive EGT in pregnancy a group of healthy pregnant women were examined

MATERIALS AND METHODS

Fifty-five healthy pregnant women were examined None of them had present or previous history of thromboembolic disease Nine were in the first trimester 19 in the second and 27 in the third trimester The analyses performed and references for the methods are given in Table I

RESULTS

The results of the coagulation studies are given in Table I The increased coagulation potential during pregnancy was reflected by high Normotest/Thrombotest values and a slight shortening of the prothrombin time A slight increase in antithrombin III was observed The most marked change was the increase in fibrinogen during late pregnancy

In all the healthy pregnant women studied only one had a positive EGT (3rd trimester) This woman later developed a deep venous thrombosis

CASE REPORTS

Case I

Born 1948 Pregnant with expected delivery March 15 1972 In November 1971 admitted to hospital with chest pains without previous symptoms of deep venous thrombosis X ray examination showed right sided pleural fluid The diagnosis of pulmonary embolism was made and the patient treated with heparin intravenously at first and later subcutaneously Initially the ethanol test was positive during i v heparin treatment it became negative After changing to subcutaneous heparin the test again became positive and intravenous treatment was reestablished On reverting to subcutaneous heparin the dose had to be fixed at 37 500 units/day to prevent a positive ethanol test On March 19th 1972 she had a normal delivery and the anticoagulant regimen was changed to warfarin This was ended in June The ethanol test remained negative after delivery No further thromboembolic complications have occurred

Case II

Born 1948 Admitted to hospital for abruptio placenta on June 11th 1972 and was delivered of a girl by caesarean section Profuse bleeding from the vagina occurred (non clotting blood) Shortly after delivery thrombocytes were 25 10^9/l fibrinogen 0 97 g/l and the ethanol test was positive The patient was treated with blood transfusion 500 ml × 6 during 4 hours In addition she received Trasylol® and purified fibrinogen 2 g Four hours after delivery thrombocytes were 63 10^9/l and fibrinogen 1 5 g/l the ethanol test was still positive Eleven hours after delivery the thrombocytes had increased to 87 5 10^9/l Fibrinogen had increased to 2 g/l and the ethanol test had become negative The next day thrombocytes were unchanged fibrinogen was 3 65 g/l and the ethanol test negative Clinically the patient improved rapidly and completely

Table I *Coagulation values in 55 healthy pregnant women*

	Ref	Normal values	Values in 55 pregnant women					
			1st trimester (9)		*2nd trimester (19)*		3rd trimester (27)	
			Mean	Range	Mean	Range	Mean	Range
Normotest (%)		65–150	97	82–130	122	92–145	125	80–150
Thrombotest (%)		50						
Thromboplastin time (sec)	(5)	13–17	15 5	13–18	14 2	13–16	14 1	11–16
Partial thromboplastin time (sec)	(10)	60–85	67 5	56–92	69 0	52–92	68 0	42–81
Antithrombin III (plasma) (%)	(6)	100–150	121	93–158	123	76–144	13	93–161
Fibrinogen (mg %)	(2)	170–400	243	147–377	25	156–382	364	65–471
Ethanol gelation test	(7)	neg	neg		neg		26 neg	1 pos

Case III

Born 1939 Pregnant with expected delivery August 24th 1972 No previous thromboembolic disease when admitted to hospital January 26th with symptoms of deep venous thrombosis in the left leg and pulmonary embolism Coagulation studies revealed signs of intravascular coagulation with consumption of thrombocytes (490–125 10^9/l) and of fibrinogen (6 3–2 35 g/l) NT/TT-discrepancy (170%/68%) and a positive ethanol test She was treated with heparin 30000 IU/day by continuous intravenous infusion The coagulation factors including the ethanol test returned to normal Several attempts to discontinue heparin during the first weeks were followed by reappearance of a postive ethanol test a drop in the fibrinogen and thrombocyte values as well as increased pain and swelling of her left leg After 6 weeks heparin was discontinued with maintenance of a negative ethanol test During delivery heparin was given subcutaneously 25000 IU/day divided into two doses As the positive ethanol test accompanied by pain in her left leg recurred the day after delivery the subcutaneous heparin treatment was continued for 5 days until a negative ethanol test was obtained Thereafter warfarin was given for 6 months Later blood samples showed no signs of hypercoagulability but phlebography 3 months after delivery showed sequelae of thrombosis in the left femoral vein

Case IV

Born 1955 Pregnant with expected delivery May 29th 1973 Admitted to hospital March 3rd with clinical signs of deep venous thrombosis in the left leg Coagulation studies revealed slight intravascular coagulation with positive ethanol test but without obvious signs of consumption of fibrinogen or thrombocytes Treatment with intravenous infusions of heparin (40–60000 IU/day) was started After 10 days heparin was administered subcutaneously 75000 IU/day divided into two doses The ethanol test became negative after weeks The patient left hospital after 18 days without medication Three days after discharge the ethanol test was again positive and treatment with heparin was reinstituted subcutaneously 50000 IU/day divided into two doses The ethanol test remained slightly positive during the rest of pregnancy but was negative the day after delivery On the first day postpartum heparin was stopped and treatment with warfarin was started and continued for 3 months Later blood samples showed no signs of hypercoagulability but phlebography 3 months after delivery revealed sequelae of thrombosis in the left femoral vein

COMMENTS

In diseases associated with a high incidence of venous thrombosis hypercoagulability as reflected by high levels of fibrinogen and other coagulation factors is regularly found In addition a positive ethanol test for fibrinemia is often observed (9) In the present study previous reports on blood changes during pregnancy were confirmed (4) In spite of this hypercoagulable state a positive ethanol test is most uncommon in normal pregnancy Thus the only woman with a positive test in the present material developed a deep vein thrombosis the day after delivery It seems therefore that a positive ethanol test is clinically significant even in late pregnancy and indicates increased risk of thromboembolic complications It is significant that increased serum levels of fibrin degradation products in pregnancy have been shown to be associated with a marked increase in postpartum thromboembolic complications (8)

In addition to its diagnostic value the ethanol test may prove useful in monitoring treatment and in detecting recurrences as shown in the above case reports It should be stressed however that the occurrence of a positive ethanol test does not always necessitate the use of anticoagulants as it was

fund in case II that intravascular coagulation may be a self limiting state when the triggering factor is removed

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Submitted for publication June 16 1977

Clas Eika M D
Avdelning IX
Ullevål Sykehus
Oslo
Norway

Acta Obstet Gynecol Scand 57 477–478 1978

A PREGNANCY WITH A HYDATIDIFORM MOLE THYREOTOXICOSIS AND LIVE BORN INFANT

Poul Ladehoff and Andrzej Maruszczak

From the Department of Obstetrics and Gynaecology Odense University Hospital and the Department of Obstetrics and Gynaecology Sønderborg Hospital Denmark

Abstract A 6-year-old woman pregnant for the 3rd time was admitted in the 2nd trimester with bleeding and slight signs of thyreotoxicosis The free thyroxin total thyroxin and TRH test confirmed the diagnosis The patient was delivered 8 weeks before term of a living boy of 1680 g Immediately after the child a 300 g normal placenta was born followed by 650 g of molar tissue

Four weeks after birth and evacuation of the molar tissue the patient was euthyreoid with normal thyreoid parameters It is presumed to have been a twin pregnancy in which the part transformed to molar tissue has secreted a thyroid stimulating factor

The majority of cases of hydatidiform mole present with symptoms in the 16th to 24th week and the course of the disease has been described as being similar to abortion (1 2 3)

The concomitant occurrence of a mole and a normally developed foetus is a rare phenomenon A survey of the literature (4 10 11) showed a frequency of approximately 1 14000 births in areas in which the incidence of hydatidiform mole is approximately 1 700 In other words the concomitant occurrence of a mole and foetus is approximately 5% of all cases of a mole

The delivery of a living infant in connection with the changes brought about by a mole occurs extremely rarely A survey from Australia covering 6 years showed 29 births of foetuses together with moles but of these only 6 were live born 5 were twin pregnancies 3 dizygotic and 2 monozygotic there was only one case of a single pregnancy (1 2)

A considerable increase in thyreoid function with or without clinical signs of hyperthyreoidism occurs in connection with hydatidiform mole (6 7 8 9 12 13) and with choriocarcinoma (6) The hyperthyreoidism disappears and the thyroid function returns to normal following chemotherapeutical treatment of the choriocarcinoma or evacuation of the mole (6 7 8 9 12)

A specific thyreoid stimulating factor that differs from long acting thyreoid stimulator has been found in molar tissue and has been termed molar thyreoid stimulating factor (5 8) However Tojo et al (12 13) are of the opinion that the thyreoid stimulating factor in molar tissue is identical to that found in normal human placentae but that it is merely secreted in abnormal amounts by the molar tissue It has been stated that human chorionic gonadotropin can induce thyreotoxicosis (7)

A case like the present one with a living infant mole and hyperthyreoidism has not been described before We therefore consider it of interest to report the case

CASE REPORT

(M L 220750) A previously healthy 26-year-old woman gravida 3 para 3 was admitted during the third pregnancy from the 12th to 14th week with vague abdominal pains and vaginal bleeding The uterus was found to be slightly larger than indicated by the menostasis and heart sounds were heard with the aid of a doptone The symptoms disappeared spontaneously She suffered from nausea and periodic vomiting during the whole of the first and part of the second trimester The patient was readmitted from the 24th week owing to vomiting loss of weight of 5 kg and spotting She was found to be restless with a warm and sweaty skin as well as having a fine tremor of the hands No exophthalmus or goiter was present The thyreoid parameters T_3-test 63–66% corresponding to a normal pregnancy free thyroxin 96 6–77.5 pmol/l (20 0–36 1) total thyroxin 324–231 nmol/l (66–139) A TRH test showed no rise in TSH values 11 2–8 1–9 0 μU/ml The results of this test together with the increased values of free thyroxin indicated that the patient suffered from thyreotoxicosis A placenta scintigraphy with Tc99m alb was carried out owing to the continued spotting This showed strange large areas of reduced activity in the placental region and a deep placental seat (Fig 1) These areas were interpreted as being infarctions The oestriol excretion in the urine showed a normal rise The membranes ruptured in the 32nd week of pregnancy

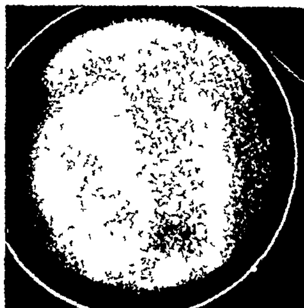


Fig 1 Placenta scintigraphy

and the patient was spontaneously delivered of a living male child without complications The birth weight was 1 680 g The placenta was delivered together with large amounts of molar tissue immediately after the child Considerable amounts of molar tissue were removed manually and with a blunt curette The placenta weighed 300 g and had no septum *The total weight of the molar tissue was* 650 g The patient was discharged from hospital 5 days after delivery Histological examination 1) underdeveloped placenta 2) hydatidiform mole A control examination 4 weeks after birth showed that the patient was euthyreoid with normal thyreoid parameters T_3 test 86% free thyroxin 19 3 pmol/l total thyroxin 85 nmol/l hCG negative The ovaries were enlarged (5–6 cm in diameter) At a control examination 6 weeks after birth the ovaries were normal The child was discharged 5 weeks after birth with a weight of ?400 g and no signs of any metabolic disease

DISCUSSION

The etiology of hydatidiform mole is unknown but it has been suggested that it is primarily a defect of the ovum (3)

In our case there could have been a twin pregnancy We have not found any septum and no chromosome analysis was carried out on the molar tissue so we cannot draw any definite conclusions about this

Unlike others (6 7 8 12 13) we were not in a position to isolate the thyroid stimulating factor But the various thyreoid parameter which clearly demonstrated that the patient was thyreotoxic were completely normal 4 weeks after removal of the molar tissue This would suggest that the mole was the cause of the condition This is in agreement with others (7 12) who found complete normalization of the parameters within the first week following evacuation Our patient had only a few clinical signs of thyreotoxicosis during the first part of he hospitalization signs which could easily have been overlooked or interpreted as normal problems w the pregnancy Such a course with slight to moderate symptoms is the most frequent (8 12) but the condition can also develop into a *life threaten* state with severe hyperthyreoidism and pulmonary oedema which disappear promptly after eva ua of the mole (6 9)

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Submitted for publica n June 6 1977

Poul Ladehoff
Karolinevej 6
5500 Middelfart
Denmark

Acta Obstet Gynecol Scand 57 479–481 1978

MYOMETRIAL ACTIVITY AND ENDOMETRIAL BLOOD FLOW IN AN ECTOPIC PREGNANCY

Mats Åkerlund

From the Department of Obstetrics and Gynaecology University Hospital Lund Sweden

Abstract Myometrial activity and endometrial blood flow were recorded in a patient with uterine haemorrhage and lower abdominal pain who turned out to have a tubal pregnancy The uterine contractions had an amplitude sometimes exceeding 400 mmHg and a duration up to 3 5 min Thus strong uterine contractions can appear during pregnancy without the presence of a gestational sac within the uterus This is contrary to the assumption that processes in the foetal membranes initiate the sequence of events leading to abortion or labour

There is an increasing amount of evidence suggesting that degenerative changes in the decidua initiate a synthesis and liberation of prostaglandins (PG) and that these PGs induce labour and abortion (cf 5) Recently Schwarz Schultz McDonald and Johnston (10) suggested that an obligatory precursor in the synthesis of PGE_2 and PGF_2 arachidonic acid is released from the foetal membranes and diffuses to the decidua Gustavii (7) on the other hand proposed that PG precursor acids are derived from phospholipids of cellular membranes in decidual cells An indirect way to study the importance of the foetal membranes as a source of PG precursors appeared during a recent study on primary dysmenorrhoea (1) Accidentally intrauterine pressure and endometrial blood flow was recorded in a woman with uterine haemorrhage and lower abdominal pain who turned out to have a tubal pregnancy

CASE REPORT

The woman investigated was a 23 year old nurse who with the exception of a moderate primary dysmenorrhoea had previously been healthy She volunteered for a study on primary dysmenorrhoea and was well informed of the experimental procedure She had never been pregnant previously but had finished the use of contraceptive pills 6 months earlier and since then she had not menstruated Conventional pregnancy tests (Pregnosticon Planotest Pharmacia AB Sweden) taken both 20 and 7 days before the recording session had been negative The patient denied any symptoms of pregnancy such as breast engorgement and morning nausea She was registered during what was assumed to be an ordinary menstruation The investigation started 48 h after the onset of a spotting vaginal bleeding and 5 h after the onset of a colicky lower abdominal pain accompanied by general symptoms of nausea and chill In a blood sample obtained at the beginning of the recording session the plasma concentration of progesterone was 0 40 ng/ml and of oestradiol 70 pg/ml determined by radioimmunoassay Myometrial activity was recorded as changes in intrauterine pressure (3) and local decidual blood flow was registered by a technique based on measuring thermoconduction from a heated thermistor to blood flow in the surrounding tissue (2)

The original recording of intrauterine pressure and blood flow in the patient one hour after the start of the recording is shown in Fig 1 The patient had regular and well-defined uterine contractions with multiple peaks The contractions varied in amplitude between 200 and 425 mmHg in duration between 2 and 3 5 min and in frequency between 2 and 4 contractions per 15 min After every contraction there was a period of uterine relaxation the basal tonus being about 25 mmHg The local endometrial blood flow decreased markedly during each contraction but resumed its previous level in between

During the recording the patient continuously reported all changes in character and intensity of her pain This was noted on the recording curve which was not visible to her It was found that the colicky pain appeared in periods which corresponded to the periods of uterine contraction and decrease in blood flow Between these periods the patient felt practically no pain

As a part of the intended study on dysmenorrhoea the selective β_2-receptor stimulator terbutaline (Bricanyl® Draco Sweden) was given after 2 h and 15 min of recording as a single intravenous injection of 0 25 mg during 2 min The drug effectively inhibited the uterine contractile activity and only a few contractions of a small amplitude appeared during 45 min of recording after the injection The local endometrial blood flow remained fairly constant after the administration of terbutaline except for decreases in flow occurring in parallel with the remaining

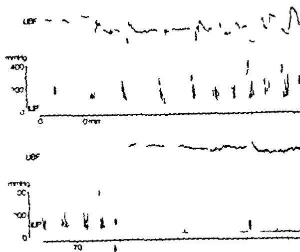


Fig 1 Local endometerial blood flow (UBF) intrauterine pressure (IUP) and the effect of terbutaline (0 25 mg i v injection indicated by arrow) in a woman with lower abdominal pain and vaginal bleeding due to an ectopic pregnancy

myometrial contractions After the injection the patient reported a total relief of her low abdominal pain and when it returned after about 2 h it was much less pronounced

During the days after the recording the woman had repeated periods of slight vaginal bleeding or spotting and also periods of moderate colicky pain Because of these symptoms she underwent laparoscopy and laparotomy 16 days after the recording An ampullary pregnancy in her right Fallopian tube was found and expelled The ovum had a diameter of about 9 mm At histopathological examination chorion villi but no embryonal structures were found

DISCUSSION

The plasma concentrations of oestradiol and progesterone at the recording corresponded to normal values in nonpregnant women during the first menstrual days (9) Consequently it can be assumed that the spotting vaginal bleeding in the present woman was the result of withdrawal of hormonal stimulation of the decidua with consequent degeneration and shedding According to the hypothesis of Gustavii and others (cf 6) this decidual degeneration may have initiated the uterine activity

The uterine activity in the present case resembled recordings from intrauterine pregnancies (e g 4) in as much as the contractions were well-defined regular and had intervening periods of complete uterine relaxation There were however important differences the most remarkable finding in the ectopic pregnancy being the extremely high amplitude and long duration of the contractions A comparison of amplitudes as an index of myometrial activity in a uterus containing a gestational sac with one that does not is however diff[illegible] since according to the law of Laplace the muscular work required to produce a certain intrauterine pressure increases with the squared radius of the intrauterine cavity In the nonpregnant uterus such high pressures were not recorded as seen in the present case not even in severe primary dysmenorrhoea (1) or after expulsion of an IUD (5)

The findings in this case of ectopic pregnancy suggest that the presence of an intrauterine gestational sac is not of importance for the induction of uterine contractions at decidual degeneration This supports the suggestion of Gustavii (7) that PG precursor acids can originate from within the decidual cells The extremely strong and long lasting uterine contractions found in the present woman are rarely seen in physiological conditions It is tempting to speculate whether this activity might be due to the lack of an inhibitory function of an intrauterine pregnancy Such a concept would be in accordance with the findings of Keirse et al (8) who in tissue from early pregnant human uterus demonstrated high concentrations of PG degradating enzymes in placenta and foetal membranes but only small concentrations of these enzymes in myometrium and decidua

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Submitted for publication Oct 26 1977

Mats Åkerlund
Department of Obstetrics and Gynecology
University Hospital
Lund
Sweden

ANNOUNCEMENT

Indian Society of Human Genetics—*V Annual Conference* including an *International Symposium on Population Structure and Human Variation* 20–24 December 1978 Bombay India Details from Dr [illegible] Institute for Research in Reproduction Bombay [illegible] India (tel [illegible])

Acta Obstet Gynecol Scand 57 483–484 1978

ANENCEPHALY AND CLOMIPHENE INDUCED PREGNANCY

Y Biale H Leventhal M Altaras and N Ben Aderet

From the Department of Obstetrics and Gynecology A The Soroka Medical Center Beersheba Israel

Clomiphene citrate is used extensively today to induce ovulation in an anovulatory female to improve fertility It is well known that the incidence of multiple pregnancies abortions and overstimulation syndrome in clomiphene induced pregnancies is higher than in non induced pregnancies (1) Recent publications indicate an association with hydatidiform mole in clomiphene related pregnancies (2 3 4) The following are two case reports of anencephalic births to mothers who had received clomiphene as an ovulatory stimulus

CASE REPORTS

Case 1 A 37 year-old woman married 12 years with no previous pregnancy Menarche at age 13 with regular periods Basal body temperature usually biphasic with normal ovulatory levels of pregnandiol Hysterosalpingography showed a normal uterus with patent tubes Since the husband was found to be totally azospermic it was decided to perform donor artificial insemination Due to the fact that pregnancy did not ensue 100 mg clomiphene citrate was given for a total of 5 days from the fifth day of the cycle Under this treatment she became pregnant The pregnancy followed a normal course until the eighth month when a diagnosis of small for dates was made Estriol levels were low at 3 000 μg/24 hours X ray examination of the abdomen showed an anencephalic fetus A spontaneous delivery occurred at the end of the ninth month

Case 2 A 6-year-old para 1 gravida 2 with irregular menstruation 30–70/4 since the age of 14 years The first pregnancy was induced by clomiphene citrate treatment and she gave birth to a boy weighing 3 800 g The present pregnancy was also induced after the third clomiphene treatment 100 mg per day for five days In the 43th week of pregnancy she was referred to the delivery room because of post maturity

The height of the uterine fundus fitted eight months of pregnancy There was breech presentation with closed cervical os Fetal movements and heart beats were normal The amnioscopy demonstrated clear amniotic fluid Estriol excretion on two subsequent days was 4 and 4 9 mg per 24 hours An abdominal X ray confirmed the suspicion of an anencephalus with breech presentation Three days after admission she delivered an anencephalic monster with complete cranio-spinal rachischisis

DISCUSSION

Most investigations are now agreed that there is multifactorial causation for anencephaly including genetic element with environmental factors Drugs that stimulate ovulation have not been included in the etiological factors of anencephaly Dayson & Kohler were the first to report anencephaly following ovulation stimulated by clomiphene in two women (5) Further sporadic case reports of anencephaly occurring with ovulation stimulation by clomiphene have appeared more recently (6 7) These observations are compatible with Boue & Boue s recent observation of the increased frequency of chromosomal anomalies in abortions after induced ovulation (8) Because of the rare association of anencephaly with ovulation induced by clomiphene it is claimed by James (9) that the defect may be related to the underlying subfertility for which the drug was administered rather than to the drug itself James offered some evidence that women who produce anencephalies are less fecund than other women On reviewing the literature we consider that the possibility of a casual relationship between ovulation stimulating treatment and central nervous system abnormalities should not be dismissed lightly but much additional evidence will be needed to establish the hypothesis

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Submitted for publication August 7 1977

Y Biale
Department of Obstetrics and Gynecology
A The Soroka Medical Center
Beersheba
Israel

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Letters Å and A—see under A letters Ø and Ö—see under O